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(54) Title: STABILIZATION OF RADIOPHARMACEUTICAL COMPOSITIONS USING HYDROPHILIC THIOETHERS AND HYDROPHILIC 6-HYDROXY CHROMANS

(57) Abstract: Radiopharmaceutical compositions which are stabilized by addition of a hydrophilic thioether, a hydrophilic 6-hydroxy-chroman derivative, or a mixture of a hydrophilic thioether and a hydrophilic 6-hydroxy-chroman derivative.

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STABILIZATION OF RADIOPHARMACEUTICAL COMPOSITIONS USING HYDROPHILIC THIOETHERS AND HYDROPHILIC 6-HYDROXY CHROMANS

The present invention relates to novel stabilizers of radiopharmaceutical compositions used for diagnosis and therapy. In particular, the invention relates to use of a hydrophilic thioether, a hydrophilic 6-hydroxy-chroman derivative, or a combination of a hydrophilic thioether with a hydrophilic 6-hydroxy-chroman derivative, to increase the shelf-life of diagnostic and therapeutic radiopharmaceuticals.

A number of radionuclides are routinely employed in nuclear medicine, both as diagnostic agents and as therapeutics. For example, ^{99m}Tc, ^{111}In, ^{18}F, and ^{201}Tl are employed as diagnostic imaging agents, and ^{131}I, ^{32}P, ^{89}Sr, and ^{153}Sm are in therapeutic use. In addition, nuclides such as ^{186}Re, ^{188}Re, ^{212}Bi, ^{213}Bi, ^{90}Y, ^{67}Cu, ^{192}Ir, ^{165}Dy, and ^{117m}Sn have been proposed as potential therapeutic agents. Such radionuclides are administered in the form of radiopharmaceutical compositions, which generally include a chelator for the nuclide. Radiopharmaceuticals may additionally include a targeting molecule such as a monoclonal antibody, an antibody fragment, or a receptor ligand. The availability of radiopharmaceuticals has significantly advanced diagnosis and treatment of a variety of diseases.

Chemical decomposition may limit a radiopharmaceutical's shelf life by decreasing the radiochemical purity of the agent over time. For example, a radiopharmaceutical containing ^{99m}Tc, ^{186}Re, or ^{188}Re may be susceptible to oxidation of the nuclide itself. In addition, the radiation emitted from a radionuclide can break chemical bonds of other components of the composition, thus causing autoradiolysis. Autoradiolysis is a particular problem when the radiopharmaceutical contains higher energy nuclides, such as β-emitters (*e.g.*, ^{186}Re, ^{188}Re, ^{90}Y, ^{131}I) and α-emitters (*e.g.*, ^{213}Bi, ^{212}Bi, ^{211}At, ^{225}Ac, ^{223}Ra).

Thus many radiopharmaceuticals require stabilizers to maximize shelf life. Such stabilizers must be non-toxic and must be able to maintain the product's radiochemical purity for an acceptable shelf-life as well as during use. In addition, an acceptable

radiopharmaceutical stabilizer must not interfere with delivery of the radionuclide to the target site.

Methods for stabilizing radiopharmaceuticals by adding gentisates are disclosed, for example, in U.S.Pat.Nos. 4,232,000; 4,233,284; 4,497,744; 5,384,113. Stabilization of radiopharmaceuticals using ascorbic acid is disclosed in U.S.Pat.Nos. 5,393,512 and 5,011,676, in WO 97/28181 and in WO 98/33531. Hydroquinone stabilizers of radiopharmaceuticals is disclosed in U.S.Pat.No. 4,229,427. Other compounds such as reductic acid, erythorbic acid, *p*-aminobenzoic acid, 4-hydroxybenzoic acid, nicotinic acid, nicotinamide, 2,5-dihydroxy-1,4-benzenedisulfonic acid, tartaric acid, inositol, and the like, have also been used to stabilize radiopharmaceutical compositions.

U.S.Pat.No. 5,384,113 discloses a method of preventing autoradiolysis of peptides radiolabeled with ^{111}In using gentisic acid or gentisyl alcohol. In addition to preventing autoradiolysis of peptides by ^{111}In, the method of U.S.Pat.No. 5,384,113 is proposed to prevent autoradiolysis of peptides by ^{67}Ga, ^{169}Yb, ^{125}I, ^{123}I, and ^{201}Tl. Two radiolabelled peptides, ^{111}In-DTPA-octreotide and ^{123}I-LHRH, were tested for autoradiolysis prevention. A monoclonal antibody, NR-Lu-10, labeled with ^{186}Re was also specifically exemplified.

As indicated in Example 1, *infra*, the present inventors have found that that when added as a component in radiopharmaceutical kit formulations, gentisic acid decreases the radiochemical purity of some ^{99m}Tc-labelled peptides, and thus is not useful as a stabilizer of some radiolabeled peptides. A need exists, therefore, for additional stabilizers of radiopharmaceuticals. A particular need exists for stabilizers of radiopharmaceuticals containing less than 70 amino acids linked by peptide bonds.

Methionine residues in proteins and polypeptides are known to oxidize to methionine sulfoxide. U.S.Pat.No. 5,272,135 discloses a method of inhibiting oxidation of a liquid or semi-liquid composition of a polypeptide containing at least one methionine residue by adding between 0.01% w/v to 0.3% w/v methionine to the composition. U.S.Pat.No. 5,272,135 teaches that the method disclosed therein is effective with a variety of polypeptides, including epidermal growth factor, insulin-like growth factor I, nerve growth factor, transforming growth factor alpha precursor, transforming growth factor beta precursor, transforming growth factor beta, fibroblast growth factor, vaccinia growth

factor, platelet derived growth factor, or methionine containing biologically active fragments or precursors of such growth factors. However, the data presented in U.S.Pat.No. 5,272,135 are limited to addition of methionine to inhibit oxidation of methionine residues present in epidermal growth factor. Lam, *et al.* (1997) *J. Pharm. Sci.* **86**, 1250-1255 disclose the use of methionine to stabilize the recombinant humanized monoclonal antibody rhuMAb HER2 in liquid formulations to prevent oxidation of methionine residues.

U.S.Pat.No. 5,358,708 discloses a method for increasing the storage stability of an aqueous formulation of granulocyte-macrophage colony stimulating factor or an interleukin by addition of a stabilizing amount of methionine, histidine, or mixtures thereof. U.S.Pat.No. 5,358,708 also discloses that chemical differences among proteins causes different proteins to become inactivated during storage at different rates and under different conditions. U.S.Pat.No. 5,358,708 further discloses that the storage-prolonging effects of methionine and histidine are not equivalent with different proteins, and that mixtures of amino acids exhibit different effects as the ratio varies, as the identity of the protein is changed, and/or as concentrations are altered.

WO 97/14430 discloses use of hydrophilic thioethers as antioxidants to prolong storage stability of aqueous formulations of proteins and peptides. The only data presented in WO 97/14430 relate to insulin-like growth factor I, a 70-amino acid peptide containing three disulfide bonds. WO 97/14430 further discloses that common antioxidants such as ascorbic acid, sodium thiosulfate, glutathione, or sodium bisulfite increased oxidation of IGF-1 or even precipitated the protein.

U.S.Pat.Nos. 3,947,473; 4,003,919; 4,018,799; and 4,026,907 disclose a variety of antioxidant hydrophilic 6-hydroxy-chroman compounds as intermediates in preparation of optically active α-tocopherol. U.S.Pat.No. 4,511,685 discloses hydrophilic 6-hydroxy-chroman derivatives and use of such derivatives to stabilize polypropylene compositions. U.S.Pat.Nos. 4,847,267 and 4,970,216 disclose use of one such hydrophilic 6-hydroxy-chroman, hydrophilic 6-hydroxy-2,5,7,8-tetramethyl-2-carboxylic acid alone or in combination with sulfur compounds, including glutathione or cysteine, as a skin treatment composition to inhibit generation of free radicals in the skin.

It has now been surprisingly found that the radiolabelling efficiency and shelf-life of peptide and non-peptide radiopharmaceutical compositions may be significantly increased by addition of a stabilizing amount of a hydrophilic thioether, a stabilizing amount of a hydrophilic 6-hydroxy-chroman derivative, or a stabilizing amount of a mixture of a hydrophilic thioether and a hydrophilic 6-hydroxy-chroman.

In the first aspect of this invention, the radiolabelling efficiency and shelf life of the radiopharmaceutical compositions are increased by the addition of a hydrophilic thioether.

In one embodiment of this first aspect, the invention provides a composition comprising a radiopharmaceutical precursor and a stabilizing amount of a hydrophilic thioether.

In another embodiment of this first aspect, the invention provides a method of stabilizing a radiopharmaceutical comprising the steps of:

a) combining a precursor of said radiopharmaceutical with a stabilizing amount of a hydrophilic thioether in a container; and

b) adding a radionuclide to the container.

In another embodiment of this first aspect, the invention provides a kit comprising a sealed vial containing a predetermined quantity of a radiopharmaceutical precursor and a stabilizing amount of a hydrophilic thioether.

In a second aspect of this invention, the radiolabelling efficiency and shelf life of the radiopharmaceutical compositions are increased by the addition of a hydrophilic 6-hydroxy-chroman derivative.

In one embodiment of this second aspect, the invention provides a composition comprising a radiopharmaceutical precursor and a stabilizing amount of a hydrophilic 6-hydroxy-chorman derivative.

In another embodiment of this second aspect, the invention provides a method of stabilizing a radiopharmaceutical comprising the steps of:

a) combining a precursor of said radiopharmaceutical with a stabilizing amount of a hydrophilic 6-hydroxy-chroman derivative in a container; and

b) adding a radionuclide to the container.

In another embodiment of this second aspect, the invention provides a kit comprising a sealed vial containing a predetermined quantity of a radiopharmaceutical precursor and a stabilizing amount of a hydrophilic 6-hydroxy-chroman derivative.

In the third aspect of this invention, the radiolabelling efficiency and shelf life of the radiopharmaceutical compositions are increased by the addition of a hydrophilic thioether and a hydrophilic 6-hydroxy-chroman derivative.

In one embodiment of this third aspect, the invention provides a composition comprising a radiopharmaceutical precursor, a hydrophilic thioether, and a hydrophilic 6-hydroxy-chroman.

In another embodiment of this third aspect, the invention provides a method of stabilizing a radiopharmaceutical comprising the steps of:

a) combining a precursor of said radiopharmaceutical with a stabilizing amount of a mixture of a hydrophilic thioether and a hydrophilic 6-hydroxy-chroman in a container; and

b) adding a radionuclide to the container.

In another embodiment of this third aspect, the invention provides a kit comprising a sealed vial containing a predetermined quantity of a radiopharmaceutical precursor and a stabilizing amount of a mixture of a hydrophilic thioether and a hydrophilic 6-hydroxy-chroman.

As defined herein, a "radiopharmaceutical" or "radiopharmaceutical composition" comprises a radionuclide, a chelator, and optionally a targeting moiety or domain.

In accordance with the invention, a "precursor" of a radiopharmaceutical is defined as comprising an unlabelled, that is, non-radioactive, reagent which may be a chelator or a chelator covalently linked to a targeting moiety or domain.

A "targeting moiety or domain" as defined herein as a moiety or domain capable of binding specifically to a site within a mammalian body such as a receptor on a cell surface. Targeting moieties or domains within the scope of the present invention include but are not limited to antibodies, antibody fragments such as Fab or $F(ab)'_2$ fragments, epitope binding complementarity determining regions derived from antibodies, peptides, growth factors or receptor binding fragments thereof, hormones, steroids, receptor binding nucleic acids, receptor binding carbohydrates including monosaccharides,

disaccharides, and oligosaccharides, receptor-binding lipids, benzodiazepines, receptor binding antibiotics, and the like.

A "stabilizing amount" is defined herein as that amount of hydrophilic thioether, hydrophilic 6-hydroxy-chroman or hydrophilic thioether/hydrophilic 6-hydroxy-chroman mixture sufficient to maintain the radiochemical purity, as measured by known methods such as those disclosed in the examples below, of a radiopharmaceutical composition relative to that of the radiopharmaceutical composition without the additive for at least 3 hours. Preferably, a clinically acceptable radiochemical purity for a radiopharmaceutical is at least 80% of the labelled undegraded radiopharmaceutical. More preferably, a clinically acceptable radiochemical purity for a radiopharmaceutical is at least 85% of the labelled undegraded radiopharmaceutical. Most preferably, a clinically acceptable radiochemical purity for a radiopharmaceutical is at least 90% of the labelled undegraded radiopharmaceutical.

Preferably, a stabilizing amount of hydrophilic thioether is in the range of about 0.1% (w/v) to about 1.5% (w/v). More preferably, a stabilizing amount of hydrophilic thioether is in the range of about 0.4% (w/v) to about 1.0% (w/v). More preferably, a stabilizing amount of hydrophilic thioether is in the range of about 0.5% (w/v) to about 1.0% (w/v).

A "hydrophilic thioether" is defined in accordance with the present invention as a compound having the general structure:

$$R—S—CH_2C(R^1R^2R^3)$$

wherein:

R is C_1 to C_4 alkyl or a C_1 to C_4 alkyl containing at least one hydrophilic group selected from –COOH, $–NH_2$, $–NHR^4$, $–NR^4{}_2$, –OH, $–SO_2R^4$, $–SOR^4$, $–SO_3H$, $–CONH_2$, $–CONHR^4$, $–CONR^4{}_2$, $–COOR^4$, $–OR^4$, $–SR^4$, $–NO_2$, $–SO_2NH_2$, $–SO_2NHR^4$, and $–SO_2NR^4{}_2$, with the proviso that, when R is methyl, the hydrophilic group is not NH_2, NHR^4, $NR^4{}_2$ or OH;

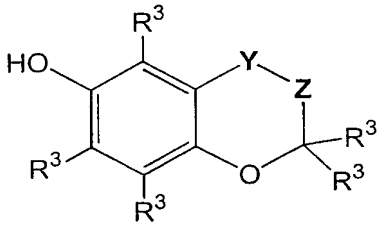
R^1, R^2, and R^3 are each independently selected from the group consisting of H, –COOH, $–NH_2$, $–NHR^4$, $–NR^4{}_2$, –OH, $–SO_2R^4$, $–SOR^4$, $–SO_3H$, $–CONH_2$, $–CONHR^4$, $–CONR^4{}_2$, $–COOR^4$, $–OR^4$, $–SR^4$, $–NO_2$, $–SO_2NH_2$, $–SO_2NHR^4$, $–SO_2NR^4{}_2$, C_1 to C_4 alkyl, and a C_1 to C_3 alkyl containing at least one hydrophilic group selected from

$-COOH$, $-NH_2$, $-NHR^4$, $-NR^4{}_2$, $-OH$, $-SO_2$; $-SO_3R^4$, $-SO_3H$, $-CONH_2$, $-CONHR^4$, $-CONR^4{}_2$, $-COOR^4$, $-OR^4$, $-SR^4$, $-NO_2$, $-SO_2NH_2$, $-SO_2NHR^4$, and $-SO_2NR^4{}_2$, with the proviso that only one of R^1, R^2, and R^3 is $-NH_2$, NHR^4, $NR^4{}_2$ or OH; and

R^4 is selected from the group consisting of C_1 to C_3 alkyl;

and with the further proviso that the hydrophilic thioether comprise at least one of said hydrophilic groups. Specific hydrophilic thioethers of the present invention include D-methionine, L-methionine, D-ethionine, L-ethionine, 3-methylthio-1,2-propanediol, methyl-3-(methylthio)propionate, 2-(ethylthio)ethylamine•HCl, 2-(methylthio)-ethanol, buthionine, S-methyl-L-cysteine, S-methyl-D-cysteine, D-methioninol, L-methioninol, and the like. Preferably, the hydrophilic thioether used in the compositions of the invention is methioninol, 2-(ethylthio)-ethylamine•HCl, 3-methythio-1,2-propanediol, or methionine. More preferably, the hydrophilic thioether used in the compositions of the invention is 2-(ethylthio)-ethylamine•HCl or methionine. Most preferably, the hydrophilic thioether used in the compositions of the invention is L-methionine.

A "hydrophilic 6-hydroxy-chroman derivative" is defined in accordance with the present invention as having a formula:



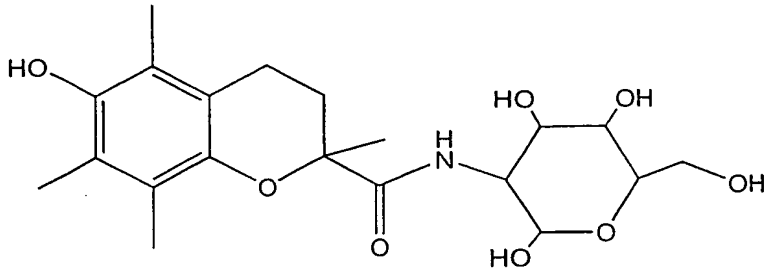
wherein one of Y and Z is selected from the group consisting of O, S, C=O, and $(CHR^3)_n$ where n is an integer from 0-3, and the other of Y and Z is selected from the group consisting of C=O and $(CHR^3)_n$ where n is an integer from 0 to 3;

each R^3 group is independently selected from the group consisting of H, alkyl, halogen, $-OR^4$, $-SO_3H$, $-SO_3R^4$, $-S(O)_mR^4$, $-COOR^4$, $-NO_2$, $-CONH_m(R^4)_{2-m}$, $-NH_m(R^4)_{2-m}$, $-COR^4$, $-CH_2OR^4$, $-COR^5$, $-SO_2NH_m(R^4)_{2-m}$, $-R^5$, and $-CH_2R^5$, where m is an integer from 0 to 2;

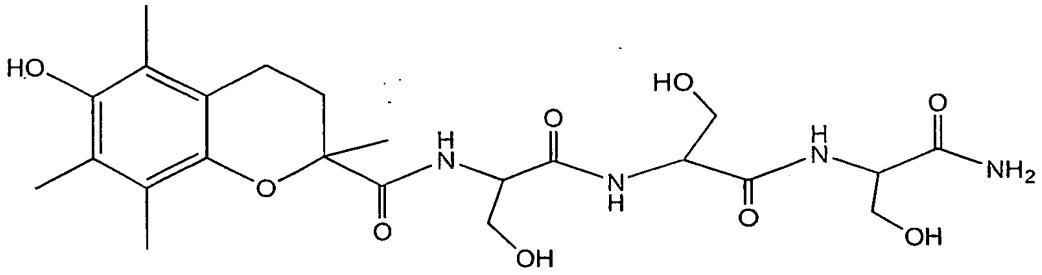
R^4 is H or C_1 to C_3 alkyl; and

R^5 is selected from the group consisting of a mono-saccharide, a disaccharide, and a hydrophilic peptide sequence of up to 5 amino acids comprising at least one hydrophilic amino acid residue.

Preferably, Y is (CH_2) and Z is (CH_2). Exemplary hydrophilic 6-hydroxy-chroman derivatives of the present invention include 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid (Trolox® , available from Aldrich Chemical Co., (Milwaukee, Wisconsin, USA); 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid-4-sulfonic acid; 6-hydroxy-2,5,7,8-tetramethylchroman-3-hydroxy-2-carboxylic acid; 6-hydroxy-2,5,7,8-tetramethylchroman-2-glucosamine, having a structure:



and 6-hydroxy-2,5,7,8-tetramethylchroman-2-(carboxy-seryl-seryl-serylamide), having the structure:



Preferably, the hydrophilic 6-hydroxy-chroman derivative of the present invention is a water soluble vitamin E derivative. More preferably, the hydrophilic 6-hydroxy-chroman derivative of the invention is a 6-hydroxy-2,5,7,8-tetramethyl-2-carboxylic acid derivative having $-CH_2$ at the 3- and 4- positions and a hydrophilic substituent at the 2-

position. Most preferably, the hydrophilic 6-hydroxy-chroman derivative of the invention is 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid.

Any radiopharmaceutical may be stabilized by addition of a hydrophilic thioether, a hydrophilic 6-hydroxy-chroman or a mixture of a hydrophilic thioether and a hydrophilic 6-hydroxy-chroman as taught herein. Ligand-type radiopharmaceuticals which do not comprise a targeting moiety or domain, such as Tc 99m MAG3 (TechnoScan®, Mallinkrodt Medical, Inc., St. Louis, Missouri, USA), may be stabilized in accordance with the present invention. In addition, radiopharmaceuticals comprising any kind of targeting moiety or domain may be stabilized in accordance with the present invention.

Recently a new class of radiopharmaceuticals has been developed which target a radiolabel to a particular tissue, disease site, or organ through a small receptor-specific molecule, which may be a peptide, a β-glucan, a benzodiazepine, or other small molecule. Such radiopharmaceuticals are disclosed and claimed, for example, in commonly assigned U.S.Pat.Nos. 5,508,020; 5,225,180; 5,405,597; 5,443,815; 5,552,525; 5,561,220; 5,620,675; 5,645,815; 5,654,272; 5,681,541; 5,711,931; 5,714,579; 5,716,596; 5,736,122; 5,770,179; 5,783,170; 5,788,960; 5,807,537; 5,807,538; 5,811,394; 5,814,297; 5,814,298; 5,814,299; 5,820,845; 5,820,846; 5,830,856; 5,833,942; 5,843,401; 5,843,403; 5,849,260; 5,849,261; 5,851,509; 5,866,097; 5,871,711; 5,932,189; 5,951,964; 5,955,426; 5,976,496; 5,997,844; 6,007,792; 6,017,509; 6,017,512; 6,028,056; 6,051,206; 6,074,627; 6,086,850; 6,171,178 and; 6,241,960; and in commonly assigned copending U.S. patent application numbers 08/236,402; 08/253,973; 08/721,443; and 09/553,494. These new agents comprise a chelator covalently linked to the receptor-specific targeting moiety or domain, and a radiolabel complexed with the chelator. A kit for making one such agent, ACUTECT®, has received approval in the U.S. for scintigraphic imaging of acute deep vein thrombosis. A second kit, NEOTECT®, has been approved in the U.S. for imaging malignant lung tumors. The stabilizers of the present invention are particularly suitable for use with radiopharmaceuticals which comprise chelators covalently linked to peptide, β-glucan, benzodiazepine, or other small targeting molecules as described in the commonly assigned patents and copending applications listed above.

In general, radiopharmaceuticals containing precursors in which a targeting moiety or domain is covalently linked to a monoamine, diamide, single thiol containing chelator such as those disclosed in commonly assigned copending U.S. patent application serial number 08/253,973 and in WO 95/33497 are stabilized using a hydrophilic thioether, a hydrophilic 6-hydroxy-chroman or a mixture of a hydrophilic thioether and a hydrophilic 6-hydroxy-chroman in accordance with this invention. In addition, radiopharmaceuticals containing precursors in which a targeting moiety or domain is covalently linked to a bisamine bisthiol (BAT) chelator such as those disclosed in commonly assigned U.S.Pat.Nos. 5,780,007; 5,776,428; 5,720,934; 5,922,303; 5,965,107; 6,086,849; and 6,093,383 and in WO 93/21962 may be stabilized in accordance with the present invention.

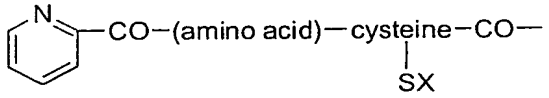
The stabilizers of the present invention may also be used for radiopharmaceuticals comprising targeting molecules covalently linked to any chelator, such as the diamine monoamide thiol chelators and the triamine thiol chelators described in U.S.Pat.No. 5,688,485 and the triamide thiols disclosed in U.S.Pat.No. 5,091,514.

The stabilizers of the invention are preferably employed to increase the shelf life of radiopharmaceuticals comprising a targeting moiety covalently linked to a peptide metal chelator having a formula

$$C(pgp)^S\text{-}(aa)\text{-}C(pgp)^S$$

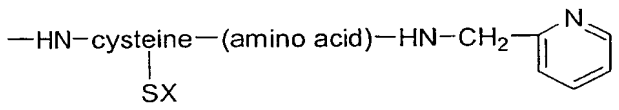
wherein $(pgp)^S$ is H or a thiol protecting group and (aa) is an amino acid. Such chelators are disclosed and claimed in commonly assigned U.S.Pat.Nos. 5,654,272; 5,681,541; 5,788,960; and 5,811,394.

The stabilizers of the invention may also be employed to increase the shelf life of radiopharmaceuticals comprising a targeting moiety covalently linked to a peptide metal chelator having a formula selected from the group consisting of:



wherein X is H or a protecting group;
(amino acid) is any amino acid;

and



wherein X is H or a protecting group;

(amino acid) is any amino acid.

Such chelators are disclosed and claimed in commonly assigned U.S. Pat. Nos. 5,720,934; 5,776,428; 5,780,007; 6,086,849 and 6,093,383.

More preferably, the stabilizers of the invention are used to increase the shelf life of radiopharmaceuticals comprising a targeting moiety covalently linked to a peptide metal chelator comprising a single thiol having a formula:

$$A\text{-}CZ(B)\text{-}[C(R'R'')]_n\text{-}X$$

wherein A is H, HOOC, H_2NOC, (peptide)-NHOC, (peptide)-OOC or R'''';

B is H, SH, -NHR''', -N(R''')-(peptide), or R'''';

X is H, SH, -NHR''', -N(R''')-(peptide) or R'''';

Z is H or R'''';

R', R'', R''' and R'''' are independently H or lower straight or branched chain or cyclic alkyl;

n is 0, 1 or 2;

and where B is -NHR''' or -N(R''')-(peptide), X is SH, and n is 1 or 2;

where X is -NHR''' or -N(R''')-(peptide), B is SH, and n is 1 or 2;

where B is H or R'''', A is HOOC, H_2NOC, (peptide)-NHOC, (peptide)-OOC, X is SH, and n is 0 or 1;

where A is H or R'''', then where B is SH, X is -NHR''' or -N(R''')-(peptide) and where X is SH, B is -NHR''' or -N(R''')-(peptide);

where X is H or R'''', A is HOOC, H_2NOC, (peptide)-NHOC, (peptide)-OOC and B is SH;

where Z is methyl, X is methyl, A is HOOC, H_2NOC, (peptide)-NHOC, (peptide)-OOC, B is SH and n is 0.

Such chelators are disclosed and claimed in commonly assigned U.S. Pat. Nos. 5,443,815; 5,807,537; 5,814,297; and 5,866,097.

Specific embodiments of the single thiol containing radiometal chelator stabilized in accordance with the present invention are described and claimed in commonly assigned copending U.S. patent application number 08/236,402 and in WO 95/29708, and include chelators having the chemical formula:

$$R^1\text{-CO-(amino acid)}^1\text{-(amino acid)}^2\text{-Z}$$

wherein (amino acid)^1 and (amino acid)^2 are each independently any primary α- or β-amino acid that does not comprise a thiol group, Z is a thiol-containing moiety selected from the group consisting of cysteine, homocysteine, isocysteine, penicillamine, 2-mercaptoethylamine and 3-mercaptopropylamine, and R^1 is lower (C^1-C^4) alkyl, an amino acid, or a peptide comprising 2 to 10 amino acids. When Z is cysteine, homocysteine, isocysteine or penicillamine, the carbonyl group of said moiety is covalently linked to a hydroxyl group, a NR^3R^4 group, wherein each of R^3 and R^4 are independently H or lower (C^1-C^4) alkyl, an amino acid or a peptide comprising 2 to 10 amino acids.

Alternatively, a single thiol containing radiometal chelator stabilized in accordance with the present invention has a formula:

$$Y\text{-(amino acid)}^2\text{-(amino acid)}^1\text{-NHR}^2$$

wherein Y is a thiol-containing moiety that is cysteine, homocysteine, isocysteine, penicillamine, 2-mercaptoacetate or 3-mercaptopropionate, (amino acid)^1 and (amino acid)^2 are each independently any primary α- or β-amino acid that does not comprise a thiol group, and R^2 is H or lower (C^1-C^4) alkyl, an amino acid or a peptide comprising 2 to 10 amino acids. When Y is cysteine, homocysteine, isocysteine or penicillamine, the amino group of said moiety is covalently linked to –H, an amino acid or a peptide comprising 2 to 10 amino acids.

Specific embodiments of the single thiol containing radiometal chelator are selected from the group consisting of:

-(amino acid)^1-(amino acid)^2-A-CZ(B)-{C(R^1R^2)}$_n$-X},

-A-CZ(B)-{C(R^1R^2)}$_n$-X}-(amino acid)^1-(amino acid)^2,

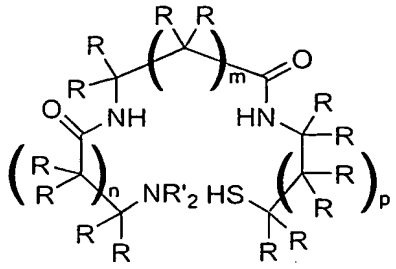
-(a primary α,ω- or β,ω-diamino acid)-(amino acid)^1-A-CZ(B)-{C(R^1R^2)}$_n$-X}, and

-A-CZ(B)-{C(R^1R^2)}$_n$-X}-(amino acid)^1-(a primary α,β- or α,ω-diamino acid) wherein the term "α,ω-diamino acid" represents an amino acid having an amine on the α carbon atom and an amine on the carbon atom most distal from the α carbon atom, the term "β,ω-diamino acid" represents an amino acid having an amine on the β carbon atom and an amine on the carbon atom most distal from the β carbon atom, and (amino acid)^1 and (amino acid)^2 are each independently any naturally-occurring, modified, substituted or altered α- or β-amino acid not containing a thiol group.

Specific single thiol-containing radiometal chelators stabilized in accordance with the invention have a formula selected from the group consisting of: -Gly-Gly-Cys-, Cys-Gly-Gly-, -(ε-Lys)-Gly-Cys-, (δ-Orn)-Gly-Cys-, -(γ-Dab)-Gly-Cys-, –(β-Dap)-Lys-Cys-, and –(β-Dap)-Gly-Cys-. (In these formulae, ε-Lys represents a lysine residue in which the ε-amino group, rather than the typical α-amino group, is covalently linked to the carboxyl group of the adjacent amino acid to form a peptide bond; δ-Orn represents an ornithine residue in which the δ-amino group, rather than the typical α-amino group, is covalently linked to the carboxyl group of the adjacent amino acid to form a peptide bond; γ-Dab represents a 2,4-diaminobutyric acid residue in which the γ-amino group is covalently linked to the carboxyl group of the adjacent amino acid to form a peptide bond; and β-Dap represents a 2,3-diaminopropionic acid residue in which the β-amino group is covalently linked to the carboxyl group of the adjacent amino acid to form a peptide bond.)

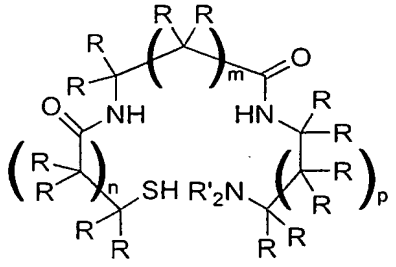
Most preferably, the stabilizers of the invention may be used to increase the shelf life of radiopharmaceuticals comprising a targeting moiety covalently linked to a monoamine, diamide, single thiol metal chelator such as those disclosed and claimed in commonly assigned copending U.S. patent application serial number 08/253,973 and in WO 95/33497, and to increase the shelf life of radiopharmaceuticals comprising a targeting moiety covalently linked to a bisamide bisthiol metal chelator such as those disclosed and claimed in commonly assigned U.S. Pat. Nos. 5,780,007; 5,922,303; 6,086,849; and 6,093,38[illegible]. Exemplary monoamine, diamide, single thiol chelators stabilized by a mixture of a hydrophilic thioether and a hydrophilic 6-hydroxy chroman have general formulae selected from the group consisting of:

(i)



and

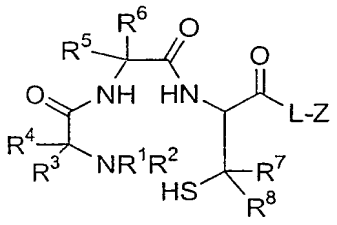
(ii)



wherein n, m and p are each integers that are independently 0 or 1; each R′ is independently H, lower alkyl, C_2-C_4 hydroxyalkyl, or C_2-C_4 alkoxyalkyl, and each R is independently H or R″, where R″ is a substituted lower alkyl group, an unsubstituted lower alkyl group, or a phenyl not comprising a thiol group, and one R or R′ is L, where L is a bivalent linker linking the metal chelator to the targeting moiety and wherein when one R′ is L, NR'_2 is an amine. In preferred embodiments, L is a C_1-C_6 linear alkyl group; a branched chain alkyl group; a cyclic alkyl group; a carboxylic ester; a carboxamide; a sulfonamide; an ether; a thioether; an amine; an alkene; an alkyne; a 1,2-linked, optionally substituted benzene ring; a 1,3-linked, optionally substituted benzene ring; a 1,4-linked, optionally substituted benzene ring; an amino acid, or a peptide of 2 to about 10 amino acids, or combinations thereof. In preferred embodiments, R″ is a C_1-C_6 linear alkyl group; a branched alkyl group; a cyclic alkyl group; a $-C_qOC_r-$, $-C_qNHC_r-$ or $-C_qSC_r-$ group, where q and r are integers each independently 1 to 5 wherein the sum of q + r is not greater than 6; a (C_1-C_6) alkyl-X, where X is a hydroxyl group; a substituted amine; a guanidine; an amidine; a substituted thiol group; a carboxylic acid; an ester; a phosphate group; a sulfate group; a phenyl group; a phenyl group substituted with a halogen, a hydroxyl, a substituted amine, a guanidine, an

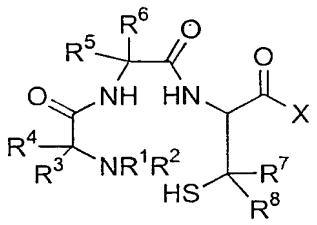
amidine, a substituted thiol, an ether, a phosphate group, or a sulfate group; an indole group; a C_1-C_6 heterocyclic group containing 1 to 3 nitrogen, oxygen or sulfur atoms; or a combination thereof.

In a specific embodiment, the monoamine, diamide single thiol radiometal chelator stabilized in accordance with the invention may have a formula:



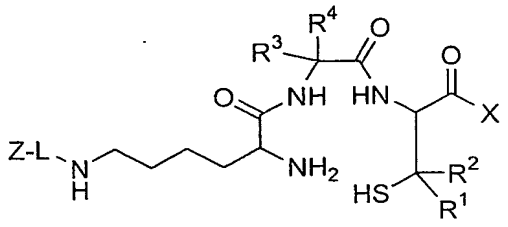
wherein R^1 and R^2 are each independently H, lower alkyl, C_2-C_4 hydroxyalkyl, or C_2-C_4 alkoxyalkyl; R^3, R^4, R^5 and R^6 are independently H, substituted or unsubstituted lower alkyl or phenyl not comprising a thiol group; R^7 and R^8 are each independently H, lower alkyl, lower hydroxyalkyl or lower alkoxyalkyl; L is a bivalent linker group and Z is a targeting moiety.

The monoamine, diamide single thiol radiometal chelator stabilized in accordance with the invention may alternatively have a formula:



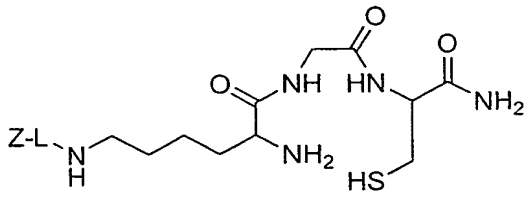
wherein R^1 and R^2 are each independently H, lower alkyl, C_2-C_4 hydroxyalkyl, or C_2-C_4 alkoxyalkyl; R^3, R^4, R^5 and R^6 are independently H, substituted lower alkyl, unsubstituted lower alkyl, phenyl, substituted phenyl not comprising a thiol group, and one of R^3, R^4. R^5 or R^6 is Z-L-HN$(CH_2)_n$-, where L is a bivalent linker, Z is a targeting moiety, and n is an integer from 1 to 6; R^7 and R^8 are each independently H, lower alkyl, lower hydroxyalkyl, lower alkoxyalkyl; and X is an amino group, a substituted amino group or -NR^1-Y, where Y is an amino acid, an amino acid amide, or a peptide comprising from 2 to 10 amino acids.

The monoamine, diamide single thiol radiometal chelator stabilized in accordance with the invention may alternatively have a formula:



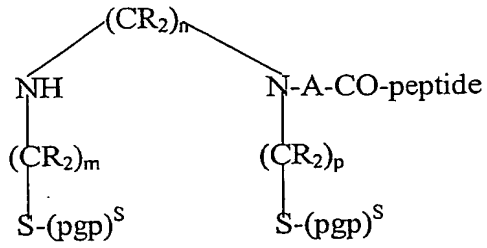
wherein R^1 and R^2 are each independently H, lower alkyl, lower hydroxyalkyl, or lower alkenylalkyl; R^3 and R^4 are independently H, substituted or unsubstituted lower alkyl or phenyl not comprising a thiol group; n is an integer from 1 to 6; L is a bivalent linker; and Z is a targeting moiety.

The monoamine, diamide single thiol radiometal chelator stabilized in accordance with the invention may alternatively have a formula:



wherein L is a bivalent linker and Z is a targeting moiety.

Bisamide bisthiol metal chelators stabilized in accordance with the present invention preferably have a formula selected from the group consisting of:



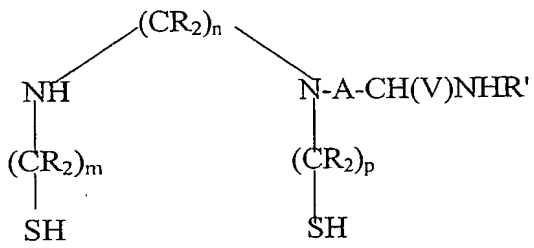
wherein each R is independently H, CH_3 or C_2H_5;

each $(pgp)^S$ is independently a thiol protecting group or H;

m, n and p are independently 2 or 3;

A is linear or cyclic lower alkyl, aryl, heterocyclyl, a combination thereof or a substituted derivative thereof;

and



wherein each R is independently H, CH_3 or C_2H_5;

m, n and p are independently 2 or 3;

A is linear or cyclic lower alkyl, aryl, heterocyclyl, a combination thereof or a substituted derivative thereof;

V is H or -CO-peptide;

R' is H or peptide;

and wherein when V is H, R' is peptide; and when R' is H, V is -CO-peptide.

For example, the stabilizers of the invention may be used to increase the shelf life of radiopharmaceuticals comprising the specific precursors set forth below:

GGCSIPPEVKFNKPFVYLI.amide (SEQ ID NO:1);

GGCSIPPEVKFNKPFVYLI (SEQ ID NO:2);

GGCGLF (SEQ ID NO:3);

RGCSIPPEVKFNKPFVYLI.amide (SEQ ID NO:4);

RGCGHRPLDKKREEAPSLRPAPPPISGGYR.amide (SEQ ID NO:5);

GGCRPKPQQFFGLM.amide (SEQ ID NO:6);

GGCFVYLI.amide (SEQ ID NO:7);

(*acetyl*.TKPRGG)$_2$K(ε-K)GC.amide;

F_DFYW$_D$KTFT(ε-K)GC.amide;

acetyl.F_DFYW$_D$KTFT(ε-K)GC.amide;

acetyl.Nal$_D$.Cpa.YW$_D$KTFT(ε-K)GCKK.amide;

acetyl.F_DFYW$_D$KTFTGGG(ε-K)GC.amide;

acetyl.$F_DFYW_DKTFTGGG(\varepsilon\text{-}K)KC$.amide;

acetyl.$KKKKK.Nal_D.Cpa.YW_DKTFT(\varepsilon\text{-}K)GC$.amide;

acetyl.$D_DF_D.Cpa.YW_DKTFT(\varepsilon\text{-}K)GCKK$.amide;

acetyl.$D_DF_D.Cpa.YW_DKTC(\varepsilon\text{-}K)GCKK$.amide;

acetyl.$KKKKK.Nal_D.Cpa.YW_DKTFT(\varepsilon\text{-}K)GCKK$.amide;

acetyl.$Nal_D.Cpa.YW_DKTFT(\varepsilon\text{-}K)GCKK$.amide;

acetyl-$DDD.Nal_D.Cpa.YW_DKTFT(\varepsilon\text{-}K)GCKK$.amide;

acetyl.$D_DDF_D.Cpa.YW_DKTFT(\varepsilon\text{-}K)GCKK$.amide;

(DTPA).$F_DFYW_DKTFT(\varepsilon\text{-}K)GC$.amide;

(DTPA).$Nal_D.Cpa..YW_DKT.Nal.T(\varepsilon\text{-}K)GCKK$.amide;

(DTPA).$(\varepsilon\text{-}K)GCF_DFYW_DKTFT$.amide;

(DTPA).$(\varepsilon\text{-}K)GCF_D.Cpa..YW_DKTFT$.amide;

(DTPA).$F_D.Cpa.YW_DKTFT(\varepsilon\text{-}K)GC$.amide;

(DTPA).$Nal_D.Cpa.YW_DKTFT(\varepsilon\text{-}K)GC$.amide;

(DTPA).Aca.$F_D.Cpa.YW_DKTFT(\varepsilon\text{-}K)GC$.amide;

(DTPA).$Nal_D.Cpa.YW_DKT.Nal.T(\varepsilon\text{-}K)GCKK$.amide;

(DTPA).$Nal_D.Cpa.YW_DKTFT(\varepsilon\text{-}K)GCKK$.amide;

$\underline{CH_2CO.FFW_DKTFC}(\varepsilon\text{-}K)GC$.amide;

$\underline{CH_2CO.FFW_DKTFC}KKKKK(\varepsilon\text{-}K)GC$.amide;

$\underline{CH_2CO.FFW_DKTFC}(\varepsilon\text{-}K)KKKKKGC$.amide;

$AKCGGGF_DFYW_DKTFT$.amide;

$AKCGGGF_DYW_DKTFT$.amide;

$DDDD.Nal_D.Cpa.YW_DKTFT(\varepsilon\text{-}K)GCKKKK$.amide;

$DDD.Nal_D.Cpa.YW_DKTFT(\varepsilon\text{-}K)GCKK$.amide;

$Nal_D.Cpa.YW_DKTFT(\varepsilon\text{-}K)GCKK$.amide;

Trc.$Nal_D.Cpa.YW_DKTFT(\varepsilon\text{-}K)GCKK$.amide;

Hca.$Nal_D.Cpa.YW_DKTFT(\varepsilon\text{-}K)GCKK$.amide;

$(Trc)_2.Nal_D.Cpa.YW_DKTFT(\varepsilon\text{-}K)GCKK$.amide;

$KKKK.Nal_D.Cpa.YW_DKTFT(\varepsilon\text{-}K)GCDDDD$.amide;

K_D.Nal_D.Cpa.YW$_D$KTFT(ε-K)GCD.amide;

K_DK.Nal_D.Cpa.YW$_D$KTFT(ε-K)GCDD.amide;

K_DKK.Nal_D.Cpa.YW$_D$KTFT(ε-K)GCDDD.amide;

K_DKK.Nal_D.Cpa.YW$_D$KTFT(ε-K)GCDD.amide;

K_DKKK.Nal_D.Cpa.YW$_D$KTFT(ε-K)GCDD.amide;

K_DKKK.Nal_D.Cpa.YW$_D$KTFT(ε-K)GCKDKD.amide;

K_DKKKF_D.Cpa.YW$_D$KTF,Nal.(ε-K)GCDDDD.amide;

K(BAT).Nal_D.C_{Me}YW$_D$KVC_{Me}T.amide

K_DDKD.Nal_D.Cpa.YW$_D$KTFT(ε-K)GCKDKD.amide;

KDKD.Nal_D.Cpa.YW$_D$KTFT(ε-K)GCKDKD.amide;

F_D.Cpa.YW$_D$KTC(ε-K)GCKK.amide;

F_D.Cpa.YW$_D$KTC(ε-K)GC.amide;

F_D.Cpa.YW$_D$KTFT(ε-K)GCKK.amide;

F_D.Cpa.YW$_D$K.Abu.Nal.T(ε-K)GC.amide;

F_D.Cpa.YW$_D$KTFTGGG(ε-K)GC.amide;

F_D.Cpa.YW$_D$KTFT(ε-K)GCR.amide;

(Trc-imide).Nal_D.Cpa.YW$_D$KTFT(ε-K)GCR.amide;

Trc.(Trc-imide).K.Nal_D.Cpa.YW$_D$KTFT(ε-K)GCRR.amide;

(Trc-imide)$_2$K.Nal_D.Cpa.YW$_D$KTFT(ε-K)GCRR.amide;

(Trc-imide)$_2$K.Nal_D.Cpa.YW$_D$KTFT(ε-K)GCR.amide;

D_DDF_D.Cpa.YW$_D$KTFT(ε-K)GCKK.amide;

$D_D$$F_D$.Cpa.YW$_D$KTFT(ε-K)GCKK.amide;

F_DFYW$_D$KTFT(ε-K)GCKK.amide;

AKCGGGF_DYW$_D$KTFT.amide;

(2-ketogulonyl).Nal_D.Cpa.YW$_D$KTFT(ε-K)GCKK.amide;

(2-ketogulonyl).F_D.Cpa.YW$_D$KTFT(ε-K)GC.amide;

cyclo-(*N*-CH_3)FYW$_D$KV.Hcy(CH_2CO.GC.Dap.Dap.amide);

cyclo-(*N*-CH_3)FYW$_D$KV.Hcy(CH_2CO.(γ-Dab)KCR.amide);

cyclo-(*N*-CH_3)FYW$_D$KV.Hcy(CH_2CO.KKKKK(ε-K)GC.amide);

cyclo-(*N*-CH_3)FYW$_D$KV.Hcy(CH_2CO).(ε-K)GCK.amide;

cyclo-(*N*-CH_3)FYW$_D$KV.Hcy(CH_2CO.(β-Dap)KCR.amide);

cyclo-(*N*-CH_3)FYW$_D$KV.Hcy(CH_2CO.(β-Dap)KCK.amide);

cyclo-(*N*-CH_3)FYW$_D$KV.Hcy(CH_2CO.(δ-Orn)GCK.amide);

cyclo-(*N*-CH_3)FYW$_D$KV.Hcy(CH_2CO.(β-Dap)GCK.amide);

cyclo-(*N*-CH_3)FYW$_D$KV.Hcy(CH_2CO.K(ε-K)KCK.amide);

cyclo-(*N*-CH_3)FYW$_D$KV.Hcy(CH_2CO.(ε-K)GCKK.amide);

cyclo-(*N*-CH_3)FYW$_D$KV.Hcy(CH_2CO).K(ε-K)GC.amide;

cyclo-(*N*-CH_3)FYW$_D$KV.Hcy(CH_2CO).(ε-K)GC.amide;

RGCQAPLYKKIIKKLLES (SEQ ID NO:8);

acetyl.KK(ε-K)GCGCGGPLYKKIIKKLLES;

acetyl.KKKKKK(ε-K)GCGGPLYKKIIKKLLES;

(CH_2CO.Y$_D$.Amp.GDCKGCG.amide)$_2$(CH_2CO)$_2$K(ε-K)GC.amide;

(CH_2CO.Y$_D$.Amp.GDCGGC$_{Acm}$GC$_{Acm}$GGC.amide)$_2$(CH_2CO)$_2$K(ε-K)GC.amide;

(CH_2CO.Y$_D$.Apc.GDCKGCG.amide)$_2$(CH_2CO)$_2$K(ε-K)GC.amide;

{(CH_2CO.Y$_D$.Apc.GDCGGCG.amide)(CH_2CO)}$_2$K(ε-K)GC.amide;

(CH_2CO.Y$_D$.Apc.GDCKGG)$_2$K(ε-K)GC.β-Ala.amide;

(CH_2CO.Y$_D$.Apc.GDCKKG)$_2$K(ε-K)GC.β-Ala.amide;

{(CH_2CO.Y$_D$.Apc.GDCG)$_2$KG}$_2$K(ε-K)GCG.amide;

(CH_2CO.Y$_D$.Apc.GDC)$_2$K(ε-K)GCG.amide;

({(CH_2CO.Y$_D$.Apc.GDCGGC$_{Acm}$GC$_{Acm}$GGC.amide)(CH_2CO)}$_2$.K)$_2$K(ε-K)GCG.amide;

{(CH_2CO.Y$_D$.Apc.GDCGGC$_{Acm}$GC$_{Acm}$GGC.amide)$_2$(CH_2CO)$_2$K}$_2$K(ε-K)GCG.amide;

(CH_2CO.Y$_D$.Apc.GDCGGC$_{Acm}$GC$_{Acm}$GGC.amide)$_2$(CH_2CO)$_2$K(ε-K)GC.amide;

HSDAVFTDNYTRLRKQMAVKKYLNSILN(ε-K)GC.amide;

HSDAVFTDNYTRLRKQMAVKKYLNSILNGGC.amide (SEQ ID NO:9);

AGCHSDAVFTDNYTRLRKQMAVKKYLNSILN.amide (SEQ ID NO:10);

HSDAVFTDNYTRLRKQMAVKKYLNSILNC(BAT).amide (SEQ ID NO:11);

CH_2CO.SNLST.HhcVLGKLSC(BAT)ELHKLQTYPRTNTGSGTP.amide (SEQ ID NO:12);

CH_2CO.SNLST.HhcVLGKLSQELHKLQTYPRTNTGSGTP(ε-K)GC.amide;

CH_2CO.SNLST.HhcVLGKLSC(CH_2CO.GGCK.amide)ELHKLQTYPRTNTGSGTP.amide;

CH_2CO.SNLST.HhcVLGKLSC(CH_2CO.(β-Dap)KCK.amide)ELHKLQTYPRTNTGSGTP.amide;

CH_2CO.SNLST.HhcVLGKLSC(CH_2CO.(ε-K)GCE.amide)ELHKLQTYPRTNTGSGTP.amide;

CH_2CO.SNLST.HcyVLGKLSC(CH_2CO.GGCK.amide)ELHKLQTYPRTNTGSGTP.amide;

CH_2CO.SNLST.HcyVLGKLSC(CH_2CO.(β-Dap)KCK.amide)ELHKLQTYPRTNTGSGTP.amide;

CH_2CO.SNLST.HcyVLGKLSC(CH_2CO.(ε-K)GCE.amide)ELHKLQTYPRTNTGSGTP.amide;

CH_2CO.SNLST.Cys.LGKLSC(CH_2CO.GGCK.amide)ELHKLQTYPRTNTGSGTP.amide;

CH_2CO.SNLST.CysVLGKLSC(CH_2CO.(β-Dap)KCK.amide)ELHKLQTYPRTNTGSGTP.amide;

CH_2CO.SNLST.CysVLGKLSC(CH_2CO.(ε-K)GCE.amide)ELHKLQTYPRTNTGSGTP.amide;

SNLST.AsuVLGKLSC(CH_2CO.(β-Dap)KCK.amide)ELHKLQTYPRTNTGSGTP.amide;

SNLST.AsuVLGKLSC(CH_2CO.(β-Dap)KCK.amide)ELHKLQTYPRTDVGAGTP.amide;

cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH_3)Hcy(CH_2CO-β-Dap-Tyr-Cys-Thr(ol));

cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH_3)Hcy(CH_2CO-β-Dap-Phe(4-F)-Cys-Thr(ol));

cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH_3)Hcy(CH_2CO-β-Dap-Phe(4-NH_2)-Cys-Thr-Ser);

cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH_3)Hcy(CH_2CO-β-Dap-Dab-Cys-Thr);

cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH_3)Hcy(CH_2CO-β-Dap-Phe(4-NH_2)-Cys-Thr);

cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH_3)Hcy(CH_2CO-β-Dap-Phe(4-NH_2)-Cys-Thr(ol));

cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH_3)Hcy(CH_2CO-β-Dap-His-Cys-Thr(ol));

cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH_3)Hcy(CH_2CO-β-Dap-Arg-Cys-Thr(ol));

cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH_3)Hcy(CH_2CO-β-Dap-Gly-Cys-Lys-NH_2);

cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH_3)Hcy(CH_2CO-β-Dap-Ser-Cys-Thr(ol));

cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH_3)Hcy(CH_2CO-β-Dap-Dab-Cys-Thr(ol));

cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH_3)Hcy(CH_2CO-β-Dap-Gly-Cys-Thr(ol));

cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH_3)Hcy(CH_2CO-β-Dap-Dab-Cys-Ser(ol));

cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH_3)Hcy(CH_2CO-Gly-Gly-Cys-Lys-NH_2);

cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH_3)Hcy(CH_2CO-Gly-Gly-Cys-Arg-NH_2);

cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH_3)Hcy(CH_2CO-Ser-Ser-Cys-Lys-NH_2);

cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH_3)Hcy(CH_2CO-Ser-Ser-Cys-Arg-NH_2);

cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH_3)Hcy(CH_2CO-Ser-Ser-Cys-Lys-Thr(ol));

cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH_3)Hcy(CH_2CO-Ser-Ser-Cys-Dap-NH_2);

cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH_3)Hcy(CH_2CO-Ser-Ser-Cys-$NH(CH_2CH_2O)_2CH_2CH_2NH_2$);

cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH_3)Hcy(CH_2CO-β-Dap-Ser-Cys-Thr-$NH(CH_2CH_2O)_2CH_2CH_2NH_2$);

cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH_3)Hcy(CH_2CO-Gly-Lys-Cys-NH_2);

cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH_3)Hcy(CH_2CO-Ser-Lys-Cys-NH_2);

cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH_3)Hcy(CH_2CO-Lys-Gly-Cys-NH_2);

cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH_3)Hcy(CH_2CO-Ser-Dab-Cys-Ser(ol));

cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH_3)Hcy(CH_2CO-Ser-Dap-Cys-NH_2);

cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH_3)Hcy(CH_2CO-Gly-Gly-Cys-His-NH_2);

cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH_3)Hcy(CH_2CO-Gly-Gly-Cys-Phe(4-NH_2)-NH_2);

cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH_3)Hcy(CH_2CO-β-Dap-Orn-Cys-Thr(ol));

cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH_3)Hcy(CH_2CO-β-Dap-Dap-Cys-Thr(ol));

cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH_3)Hcy(CH_2CO-β-Dap-Lys-Cys-Thr(ol));

cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH_3)Hcy(CH_2CO-Ser-Ser-Cys-$NHCH_2CH_2OCH_2CH_2NH_2$);

cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH_3)Hcy(CH_2CO-β-Dap-Lys-Cys-NH_2);

cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH_3)Hcy(CH_2CO-δ-Orn-Gly-Cys-NH_2); and

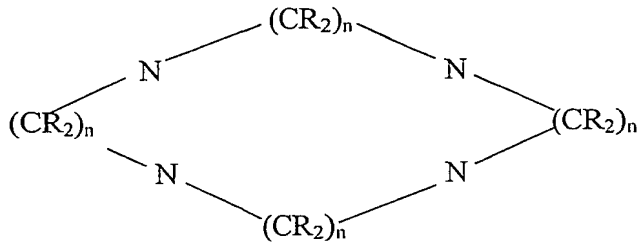
cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH_3)Hcy(CH_2CO-Thr-Gly-Gly-Cys-NH_2).

(Single-letter and three-letter abbreviations for amino acids can be found in G. Zubay, *Biochemistry* (2d. ed.), 1988 (MacMillan Publishing: New York) p.33; other abbreviations are as follows: Acm is acetamidomethyl; Mob is 4-methoxybenzyl; Abu is aminobutyric acid; F_D is D-phenylalanine; W_D is D-tryptophan; Y_D is D-tyrosine; Aca is 6-aminohexanoic acid; Apc is *S*-(3-aminopropyl)cysteine; Hcy is homocysteine; Nal is 2-naphthylalanine; Cpa is 4-chlorophenylalanine; K_D is D-lysine; D_D is D-aspartate; Nal_D is D-2-naphthylalanine; DTPA is diethylenetriaminepentaacetic acid; Trc is tricarballylic acid; Trc-imide is tricarballylic imide; and Hca is hexacarboxycyclohexane. $(...)_2K$ represents covalent linkage to both amino groups of lysine. Hcy(...) represents covalent linkage to the

sidechain sulfur atom of homocysteine. (N-CH_3)F represents N-α-methyl-phenylalanine. Underlining between groups (*e.g.*, as between the CH_2CO. group and cysteine (C) in $CH_2CO.Y_DRGDC$) represents a cyclic sulfide. Underlining between amino acids (*e.g.*, as between the cysteines (C) in CNPRGDC) represents a cyclic disulfide bond. The term "*cyclo*" before an underlined sequence means an N-terminus-to-C-terminus cyclic sequence. The subscript X_D indicates the amino acid is in the D-configuration; all other subscripts refer to amino acid sidechain protecting groups. ε-K, δ-Orn, γ-Dab, and β-Dap are defined as set forth above. Asu is 2-amino suberic acid, wherein the amino terminal amino acids of peptides containing an Asu residue are cyclized *via* an amide bond between the amino terminal amino group and the side chain carboxylic acid moiety of the Asu residue. BAT is N^6, N^9-*bis*(2-mercapto-2-methylpropyl)-6,9-diazanonanoic acid.

In accordance with the present invention, a hydrophilic 6-hydroxy-chroman derivative may also be used to stabilize labelld radiopharmaceutical precursors comprising a benzodiazepine derivative, such as those described in U.S.Pat.No. 6,171,578. In a preferred embodiment, a hydrophilic 6-hydroxy-chroman derivative such as 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid is used to stabilize radiolabelled 1-[(carboxyglycyl-glycyl-glycyl-cysteinamide)methyl]-4-(2-carboxyethyl)-7-[(4-amidinophenyl)methyl]-3,4-dihydro-1H-1,4-benzodiazepine-2,5-dione trifluoroacetate.

In addition, a hydrophilic thioether, or hydrophilic 6-hydroxy-chroman or a mixture of a hydrophilic thioether and a hydrophilic 6-hydroxychroman derivative may be used in accordance with the present invention to stabilize labelled radiopharmaceutical precursors comprising a targeting moiety or domain covalently linked to the known chelators 1,4,7,10-tetraazadodecanetetraacetic acid and derivatives thereof:



where n is an integer that is 2 or 3 and where each R is independently H, C_1 to C_4 alkyl, or aryl and one R is covalently linked to the targeting moiety, and desferrioxamine.

A radiopharmaceutical comprising any radionuclide or radiometal may be stabilized in accordance with the present invention. For example, radiopharmaceuticals containing such nuclides as ^{125}I, ^{131}I, ^{211}At, ^{47}Sc, ^{67}Cu, ^{72}Ga, ^{90}Y, ^{153}Sm, ^{159}Gd, ^{165}Dy, ^{166}Ho, ^{175}Yb, ^{177}Lu, ^{186}Re, ^{188}Re, ^{212}Bi, ^{213}Bi, ^{68}Ga, ^{99m}Tc, ^{111}In, and ^{123}I, and the like may be stabilized by addition of a hydrophilic thioether in accordance with the invention. The extent of stabilization of a particular radiopharmaceutical precursor when chelated to different radionuclides may vary. For example, a ^{99m}Tc-labelled precursor may be stabilized to a greater extent than a ^{188}Re-labelled form of the same precursor.

The compositions of the invention are formulated as a sterile, pyrogen-free, parenterally acceptable aqueous solution which may optionally be supplied in lyophilized form and be reconstituted by the user. The compositions of the invention may be provided as components of kits which may include buffers, additional vials, instructions for use, and the like.

The pharmaceutical compositions of the invention comprises a radiopharmaceutical precursor in combination with a stabilizing amount of a hydrophilic thioether, a hydrophilic 6-hydroxy-chroman or a mixture of a hydrophilic thioether and hydrophilic 6-hydroxy-chroman, optionally with a pharmaceutically acceptable diluent or a carrier such as species appropriate albumin. As used herein, a "pharmaceutically acceptable diluent or carrier" may include any and all solvents, dispersion media, antibacterial and antifungal agents, isotonic agents, enzyme inhibitors, transfer ligands such as glucoheptonate, tartrate, citrate, or mannitol, and the like. The use of such media and agents for pharmaceutically active substances is well known in the art. For example, Sodium Chloride Injection and Ringer's Injection are commonly used as diluents. The preparation of such parenterally acceptable solutions, having due regard to pH, isotonicity, stability, and the like, is within the skill in the art.

In accordance with the method of this invention, radiopharmaceuticals are preferably administered intravenously in a single unit dose, either totally as a bolus or partly as a bolus followed by infusion over 1-2 hours. The amount of solution to be injected at unit dosage is from about 0.01 mL to about 10 mL, containing about 0.01 mCi to about 100 mCi of

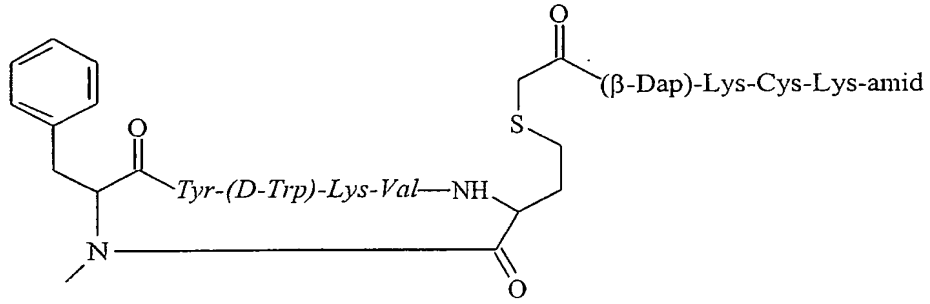
radioactivity, preferably from about 1 mCi to about 50 mCi. The amount of the radiopharmaceutical in the unit dose may range from about 0.1 to about 10 mg/kg body weight, After intravenous administration, the site is monitored, for example, by radioimaging *in vivo* if the radiopharmaceutical is a diagnostic agent.

The following examples are shown by way of illustration and not be considered as limitations.

EXAMPLE 1

Effect of Gentisic Acid on Radiochemical Purity of ^{99m}Tc-labelled Depreotide

Gentisic acid (GA) was tested for its ability to stabilize the ^{99m}Tc-labelled somatostatin receptor-binding peptide depreotide, which has the structure.



This peptide is represented as:

cyclo(*N*-CH_3)FYW$_D$KV.Hcy.(CH_2CO.(β-Dap)KCK.amide)

in the listing set forth above.

Lyophilized kit vials were prepared containing depreotide, GA, and other components as described in Table 1. Formulations were adjusted to pH 7.4 or 8.5 (as noted) prior to lyophilization.

TABLE 1

Component	Control	GA I	GA II	GA III
Depreotide	50 µg	50 µg	50 µg	50 µg
Sodium Glucoheptonate Dihydrate[1]	25 mg	25 mg	5 mg	25 mg
Edetate Disodium Dihydrate[2]	100 µg	100 µg	100 µg	100 µg
Stannous Chloride Dihydrate[3]	50 µg	50 µg	50 µg	50 µg

Gentisic Acid Sodium Salt Hydrate[4]	-	1 mg	1 mg	1 mg
pH	7.4	7.4	7.4	8.5

[1]Pfanstiehl Laboratories, Waukegan, Illinois, USA.
[2]J.T. Baker, Phillipsburg, New Jersey, USA.
[3]Acros Organics/Fisher Scientific, Pittsburgh, Pennsylvania, USA.
[4]Sigma Chemical Co., St. Louis, Missouri,USA.

The lyophilized kits were radiolabelled with ^{99m}Tc by reconstitution with 1.0 mL technetium ^{99m}Tc sodium pertechnetate (Technelite® Molybdenum Mo99-Technetium Tc99m Generator, DuPont, Billerica, Massachusetts) containing approximately 50 mCi ^{99m}Tc and heating in a boiling water bath for 10 minutes. Radiolabelling yield (RCP) results as measured by reversed phase HPLC are given in Table 2.

TABLE 2

	HPLC RCP (%)		
Formulation	**0.5 hr**	**3.5 hr**	**6.5 hr**
Control	94.5	88.3	86.4
	94.2	92.1	90.8
	94.5	91.7	90.1
(Average ± 1SD):	(94.4 ± 0.2)	(90.7 ± 2.1)	(89.1 ± 2.4)
GA I	82.4	79.4	77.2
GA II	29.1	25.1	20.5
GA III	0.9	0.7	0.6

These results indicate that gentisic acid decreases the radiolabelling yield and the stability of ^{99m}Tc-depreotide when included in formulated kits.

EXAMPLE 2

Stabilization of ^{99m}Tc-labelled Depreotide by L-Methionine

Lyophilized kit vials were prepared containing depreotide, L-methionine (Met), and other components as described in Table 3. All formulations were adjusted to pH 7.4 prior to lyophilization.

TABLE 3

Component	Control	Met I	Met II	Met III	Met IV	Met V

Depreotide	50 μg	50 μg	50 μg	50 μg	50 μg	50 μg
Sodium Glucoheptonate Dihydrate	5 mg	5 mg	5 mg	5 mg	5 mg	5 mg
Edetate Disodium Dihydrate	100 μg	100 μg	100 μg	100 μg	100 μg	100 μg
Stannous Chloride Dihydrate	50 μg	50 μg	50 μg	50 μg	50 μg	50 μg
L-Methionine USP[1]	-	1 mg	2 mg	4 mg	5 mg	10 mg

[1]Sigma Chemical Co., St. Louis, Missouri, USA.

The lyophilized kits were radiolabelled with ^{99m}Tc by reconstitution with 1.0 mL technetium ^{99m}Tc sodium pertechnetate (Technelite®) containing approximately 50 mCi ^{99m}Tc and heating in a boiling water bath for 10 minutes. Some of the formulations were also radiolabelled in a room temperature preparation (allowed to stand at rom temperature 30 minutes following reconstitution). Radiolabelling yield (RCP) results as measured by reversed phase HPLC are given in Table 4.

TABLE 4

		HPLC RCP (%)		
Formulation	**Prep Type**	**0.5 hr**	**3.5 hr**	**6.5 hr**
Control	Heated	91.9	85.0	80.7
	Heated	-	81.6	79.3
(Average):		(91.9)	(83.3)	(80.0)
	Rm Temp	94.8	87.6	78.2
	Rm Temp	90.7	88.7	83.4
(Average):		(92.8)	(88.2)	(80.8)
Met I (1 mg)	Heated	95.9	91.5	89.5
Met II (2 mg)	Heated	95.2	93.2	90.5
Met III (4 mg)	Heated	95.9	93.5	92.2
	Heated	92.4	88.5	87.4
(Average):		(94.2)	(91.0)	(89.8)
	Rm Temp	90.4	90.0	89.4
	Rm Temp	89.9	89.9	89.7
	Rm Temp	91.4	87.9	83.1
(Average ± 1SD):		(90.6 ± 0.8)	(89.3 ± 1.2)	(87.4 ± 3.7)
Met IV (5 mg)	Heated	93.8	93.7	93.5
	Heated	-	92.5	92.7
(Average):		(93.8)	(93.1)	(93.1)
Met V (10 mg)	Heated	94.5	94.6	92.6

These results indicate that L-methionine increases the radiolabelling yield and the stability of ^{99m}Tc-depreotide prepared from formulated kits which have been stored under normal conditions (≤ −10°C).

EXAMPLE 3

Stabilization of ^{99m}Tc-labelled Depreotide by L-Methionine in Lyophilized Kit Preparations; Accelerated Temperature (40°C) Storage

Lyophilized kits were prepared containing depreotide, L-methionine (Met), and other components as described in Table 5. All formulations were adjusted to pH 7.4 prior to lyophilization. The kits were stored for one week at 40°C. Some kits were also stored at -10°C as controls.

TABLE 5

Component	Control	Met
Depreotide	50 µg	50 µg
Sodium Glucoheptonate Dihydrate	5 mg	5 mg
Edetate Disodium Dihydrate	100 µg	100 µg
Stannous Chloride Dihydrate	50 µg	50 µg
L-Methionine USP	-	5 mg

The lyophilized kits were radiolabelled with ^{99m}Tc by reconstitution with 1.0 mL technetium ^{99m}Tc sodium pertechnetate (Technelite®) containing approximately 50 mCi ^{99m}Tc and incubation in a boiling water bath (10 min). Radiolabelling yield (RCP) results as measured by reversed phase HPLC are given in Table 6.

TABLE 6

			HPLC RCP (%)		
Formulation	**Storage Temp**	**Prep Type**	**0.5 hr**	**3.5 hr**	**6.5 hr**
Control	-10°C	Heated	-	82.6	77.8
	40°C	Heated	-	82.6	79.0
Met	40°C	Heated	76.5	78.0	77.6

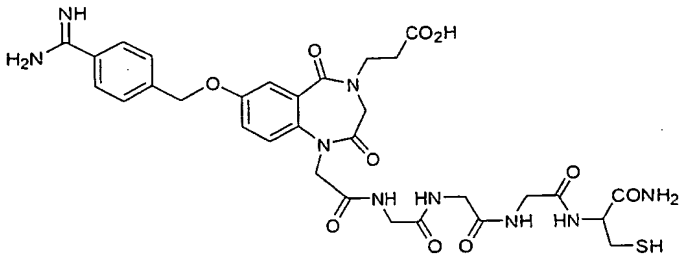
These results indicate that L-methionine does not stabilize ^{99m}Tc-depreotide in lyophilized kits which have been stored at 40°C prior to radiolabelling.

5

EXAMPLE 4

Stabilization of ^{99m}Tc-labelled Benzodiazepinedione Derivative by L-Methionine in Lyophilized Kit Preparations

L-methionine was tested for its ability to stabilize a ^{99m}Tc-labelled glycoprotein IIb/IIIa receptor-binding benzodiazepinedione derivative 1-[(carboxyglycyl-glycyl-glycyl-cysteinamide)methyl]-4-(2-carboxyethyl)-7-[(4-amidinophenyl)methyl]-3,4-dihydro-1H-1,4-benzodiazepine-2,5-dione trifluoroacetate, having the structure.



Lyophilized kit vials were prepared containing the benzodiazepinedione derivative and components as described in Table 7. All formulations were adjusted to pH 7.4 prior to lyophilization.

TABLE 7

Component	Control	Met
Derivative	40 µg	40 µg
Sodium Glucoheptonate Dihydrate	25 mg	25 mg
Edetate Disodium Dihydrate	100 µg	100 µg
Stannous Chloride Dihydrate	50 µg	50 µg
L-Methionine USP	-	5 mg

The lyophilized kits were radiolabelled with ^{99m}Tc by reconstitution with 1.0 mL technetium ^{99m}Tc sodium pertechnetate (Technelite®) containing approximately 50 mCi

^{99m}Tc and heating in a boiling water bath for 10 minutes. Radiolabelling yield (RCP) results as measured by reversed phase HPLC are given in Table 8.

TABLE 8

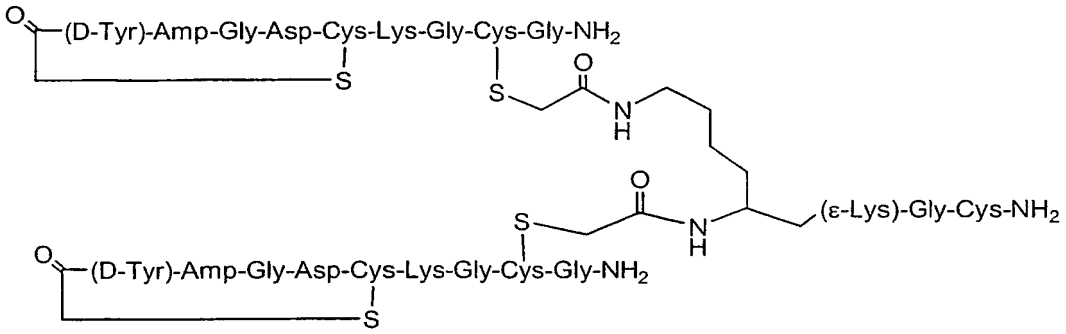
	HPLC RCP (%)		
Formulation	**0.5 hr**	**3.5 hr**	**6.5 hr**
Control	93.2	90.1	88.0
	93.6	94.5	88.8
	92.4	89.2	88.1
	85.0	86.1	82.3
(Average ± 1SD):	(91.0 ± 4.1)	(90.0 ± 3.5)	(86.8 ± 3.0)
Met (5 mg)	92.5	91.1	91.4
	93.9	92.5	91.9
	94.3	92.4	91.0
	90.5	91.2	91.9
(Average ± 1SD):	(92.8 ± 1.7)	(91.8 ± 0.8)	(91.6 ± 0.4)

These results indicate that L-methionine increases the radiolabelling yield and the stability of the ^{99m}Tc-labelled benzodiazepinedione derivative prepared from formulated kits.

EXAMPLE 5

Stabilization of Tc 99m-labelled Peptide by L-Methionine

L-methionine was tested for its ability to stabilize a ^{99m}Tc-labelled glycoprotein IIb/IIIa receptor-binding peptide having the structure.



This peptide is represented as:

$(\underline{CH_2CO.Y_D.Amp.GDC}.KGCG.amide)_2(CH_2CO)_2K(\varepsilon\text{-}K)GC.amide$

in the listing set forth above.

Lyophilized kit vials were prepared containing the peptide (50 μg), sodium glucoheptonate dihydrate (10 mg), stannous chloride dihydrate (50 μg), and edetate disodium dihydrate (100 μg). The formulation was adjusted to pH 7.4 prior to lyophilization.

The lyophilized kits were radiolabelled with ^{99m}Tc in the presence and absence of L-methionine. To the Met preparation was added 4 mg methionine (in 100 μL saline) and 100 μL ethanol. To the control preparation was added 100 μL ethanol and 100 μL saline to account for the additional saline or ethanol added with the L-methionine. Both vials were then reconstituted with 1.0 mL technetium ^{99m}Tc sodium pertechnetate (Technelite®) containing approximately 50 mCi ^{99m}Tc and allowed to incubate for 30 minutes at room temperature. Radiolabelling yield (RCP) results as measured by reversed phase HPLC are given in Table 9.

TABLE 9

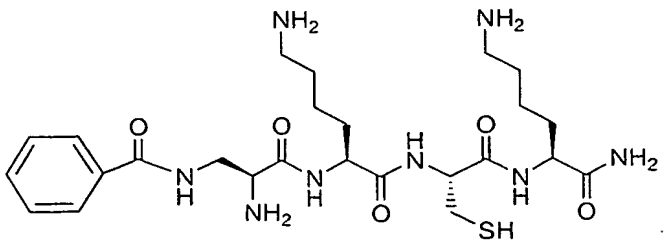
	HPLC RCP (%)		
Preparation	**0.5 hr**	**3.5 hr**	**6.5 hr**
Control	91.8	80.4	76.2
Methionine (4 mg)	96.7	96.9	96.2

These results show that L-methionine increases the radiolabelling yield and the stability of the ^{99m}Tc-peptide.

EXAMPLE 6

Stabilization of ^{99m}Tc-labelled Peptide Chelator by L-Methionine

L-methionine was tested for its ability to stabilize a ^{99m}Tc-labelled monoamine, diamide, single thiol peptide chelator having the structure.



N-3-benzoyl-2,3-(S)-diaminopropionyl-L-lysinyl-L-cysteinyl-L-lysinyl amide

Lyophilized kit "placebo" vials were prepared containing sodium glucoheptonate dihydrate, edetate disodium dihydrate, and stannous chloride dihydrate at the concentrations set forth in Table 1 (control formulation).

The peptide chelator was radiolabelled with ^{99m}Tc in the presence and absence of L-methionine. The peptide chelator was dissolved in water at a concentration of 1 mg/mL, and 50 μg (50 μL) of the peptide was added to each of three placebo vials. Ethanol and L-methionine were added to the control and methionine preparations as described in Example 5. In addition, 100 μL phosphate buffered saline (PBS) was added to each preparation. The vials were reconstituted with 0.9-1.0 mL ^{99m}Tc sodium pertechnetate (Technelite®) containing approximately 50 mCi ^{99m}Tc, and heated in a boiling water bath for ten minutes. Radiolabelling yield (RCP) results as measured by reversed phase HPLC are given in Table 10.

TABLE 10

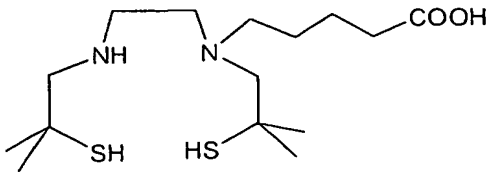
	HPLC RCP (%)			
Preparation	**0.5 hr**	**3 hr**	**6 hr**	**9 hr**
Control	94.1	92.4	85.9	80.0
L-Methionine (4 mg)	98.4	97.2	95.5	92.8

These results show that L-methionine increases the radiolabelling yield and the stability of a ^{99m}Tc-labelled peptide chelator.

EXAMPLE 7

Stabilization of a ^{99m}Tc Bisamine Bisthiol Chelator by L-Methionine

L-methionine was tested for its ability to stabilize a ^{99m}Tc-labelled non-peptide chelator (4-(butanoic acid)-2,2,9,9 tetramethyl-4,7-diaza-1,10-decanedithiol) having the structure.



The non-peptide chelator was radiolabelled with ^{99m}Tc in the presence and absence of L-methionine using the placebo vial heated preparation procedure as described in Example 6. Radiolabelling yield (RCP) results as measured by reversed phase HPLC are given in Table 11.

TABLE 11

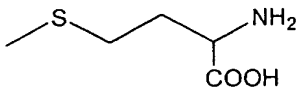
	HPLC RCP (%)			
Preparation	**0.5 hr**	**3 hr**	**6 hr**	**9 hr**
Control	48.5	56.5	54.0	52.9
Methionine (4 mg)	66.7	70.0	70.8	70.4

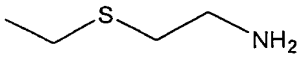
These results show that L-methionine increases the radiolabelling yield and the stability of a ^{99m}Tc-labelled non-peptide chelator.

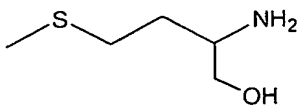
EXAMPLE 8

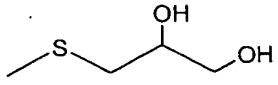
Stabilization of a ^{99m}Tc-labelled Peptide by Methionine Derivatives

2-(Ethylthio)ethylamine, methioninol, and 3-methylthio-1,2-propanediol are hydrophilic thioethers having the structures.

Methionine 

2-(Ethylthio)ethylamine 

Methioninol 

3-Methylthio-1,2-propanediol 

These compounds and L-methionine were tested for their ability to stabilize ^{99m}Tc-labelled depreotide.

Each hydrophilic thioether was dissolved in water made up at 40 mg/mL and adjusted to pH 7 with HCl or NaOH. Each hydrophilic thioether (4 mg in 100 μL) was added to a formulated kit vial containing the peptide ("control" formulation in Table 1). To the control vials were added 100 μL water. The vials were reconstituted with 1.0 mL ^{99m}Tc sodium pertechnetate (Technelite®) containing approximately 50 mCi ^{99m}Tc and heated in a boiling water bath for ten minutes. Radiolabelling yield (RCP) results as measured by reversed phase HPLC are given in Table 12.

TABLE 12

Additive	Initial RCP	3.5 hr RCP	6.5 hr RCP
Day 1:			
None (Control 1)	89.8	82.9	79.4
Methionine	95.0	90.4	89.3
2-(Ethylthio)ethylamine	92.8	94.2	93.3
Day 2:			
None (Control 2)	89.9	78.0	74.4
Methioninol	94.1	93.9	90.7
3-Methylthio-1,2-propanediol	89.1	84.0	80.9

These results show that the hydrophilic thioethers 2-(ethylthio)ethylamine, methioninol, and 3-methylthio-1,2-propanediol increase the radiolabelling yield and the stability of a ^{99m}Tc-labelled peptide. Methionine sulfoxide, methionine sulfone, and 3-(methylthio)propionaldehyde had no effect on ^{99m}Tc-labelled peptide radiolabelling yield or stability.

EXAMPLE 9

Stabilization of ^{99m}Tc-labelled Depreotide by Trolox®

Lyophilized kit vials were prepared containing depreotide, Trolox®, and other components as described in Table 13. All formulations were adjusted to pH 7.4 prior to lyophilization.

TABLE 13

Component	Control	Trolox I	Trolox II	Trolox III	Trolox IV
Depreotide	50 µg	50 µg	50 µg	50 µg	50 µg
Sodium Glucoheptonate Dihydrate	5 mg	5 mg	5 mg	5 mg	5 mg
Edetate Disodium Dihydrate	100 µg	100 µg	100 µg	100 µg	100 µg
Stannous Chloride Dihydrate	50 µg	50 µg	50 µg	50 µg	50 µg
Trolox	-	0.6 mg	1 mg	2 mg	5 mg

The lyophilized kits were radiolabelled with ^{99m}Tc by reconstitution with 1.0 mL technetium ^{99m}Tc sodium pertechnetate (Technelite®) containing approximately 50 mCi ^{99m}Tc and incubation at room temperature for 30 minutes following reconstitution. Some of the formulations were also radiolabelled in a heated preparation (heat in a boiling water bath for 10 minutes). Radiolabelling yield (RCP) results as measured by reversed phase HPLC are given in Table 14.

Table 14

		HPLC RCP (%)		
Formulation	**Prep Type**	**0.5 hr**	**3.5 hr**	**6.5 hr**
Control	Heated	92.0	85.9	84.5
	Heated	91.4	85.3	78.3
(Average):		(91.7)	(85.6)	(81.5)
	Rm Temp	92.0	85.0	84.2
	Rm Temp	92.6	85.2	80.7
	Rm Temp	92.0	81.4	79.5
	Rm Temp	89.5	82.8	-
(Average ± 1SD):		(91.5 ± 1.4)	(83.6 ± 1.8)	(81.5 ± 2.4)
Trolox I (600 μg)	Rm Temp	94.3	93.2	92.0
	Rm Temp	91.8	88.6	89.1
(Average):		(93.1)	(90.9)	(90.6)
Trolox II (1 mg)	Rm Temp	91.3	89.6	91.0
	Rm Temp	92.9	91.8	92.5
	Rm Temp	94.1	93.2	91.1
(Average ± 1SD):		(92.8 ± 1.4)	(91.5 ± 1.8)	(91.5 ± 0.8)
Trolox III (2 mg)	Heated	94.9	91.1	85.6
	Heated	95.3	92.9	88.7
(Average):		(95.1)	(92.0)	(87.2)
	Rm Temp	95.4	94.8	95.4
	Rm Temp	94.5	93.7	93.8
	Rm Temp	95.5	-	92.2
	Rm Temp	93.8	91.7	92.4
	Rm Temp	94.8	92.4	93.0
	Rm Temp	-	94.6	93.5
(Average ± 1SD):		(94.8 ± 0.7)	(93.4 ± 1.4)	(93.4 ± 1.2)
Trolox IV (5 mg)	Rm Temp	93.3	92.0	-
	Rm Temp	92.1	94.8	93.8
(Average):		(92.7)	(93.4)	(93.8)

These results indicate that Trolox® increases the radiolabelling yield and the stability of ^{99m}Tc depreotide prepared from formulated kits.

EXAMPLE 10

Stabilization of ^{99m}Tc Depreotide by Trolox® in Lyophilized Kit Preparations; Accelerated Temperature (40°C) Storage

Lyophilized kits were prepared containing depreotide, Trolox®, and other components as described in Table 15. All formulations were adjusted to pH 7.4 prior to lyophilization. The kits were stored for one week at 40°C. Some kits were also stored at -10°C as controls.

TABLE 15

Component	Control	Trolox
Depreotide	50 µg	50 µg
Sodium Glucoheptonate Dihydrate	5 mg	5 mg
Edetate Disodium Dihydrate	100 µg	100 µg
Stannous Chloride Dihydrate	50 µg	50 µg
Trolox®	-	2 mg

The lyophilized kits were radiolabelled with ^{99m}Tc by reconstitution with 1.0 mL technetium ^{99m}Tc sodium pertechnetate (Technelite®) containing approximately 50 mCi ^{99m}Tc and incubation either at room temperature (30 minutes) or in a boiling water bath (10 min). Radiolabelling yield (RCP) results as measured by reversed phase HPLC are given in Table 16.

TABLE 16

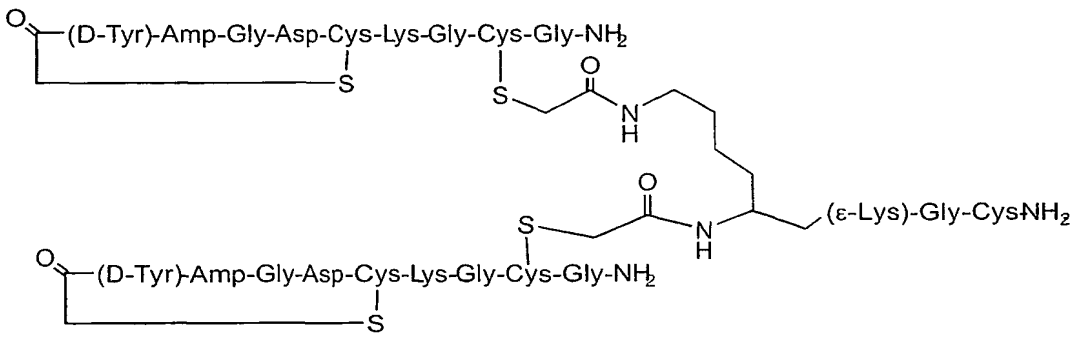
			HPLC RCP (%)		
Formulation	**Storage Temp**	**Prep Type**	**0.5 hr**	**3.5 hr**	**6.5 hr**
Control	-10°C	Heated	-	82.6	77.8
	40°C	Heated	-	82.6	79.0
Trolox®	-10°C	Rm Temp	94.4	92.9	92.3
	40°C	Rm Temp	86.6	89.2	88.6

These results indicate that the Trolox® stabilizes ^{99m}Tc-depreotide prepared from lyophilized kits which had been thermally stressed under conditions of accelerated temperature storage.

EXAMPLE 11

Stabilization of a ^{99m}Tc -labelled Peptide by Trolox

Trolox® was tested for its ability to stabilize a ^{99m}Tc-labelled glycoprotein IIb/IIIa receptor-binding peptide having the structure.



This peptide is represented as:

$(\underline{CH_2CO.Y_D.Amp.GDC}.KGCG.amide)_2(CH_2CO)_2K(\varepsilon\text{-}K)GC.amide$

in the listing set forth above.

Lyophilized kit vials were prepared containing the peptide (50 μg), sodium glucoheptonate dihydrate (10 mg), stannous chloride dihydrate (50 μg), and edetate disodium dihydrate (100 μg). The formulation was adjusted to pH 7.4 prior to lyophilization.

The lyophilized kits were radiolabelled with ^{99m}Tc in the presence and absence of Trolox®. To the Trolox® preparation was added 2 mg Trolox® in 100 μL ethanol and 100 μL saline. The ethanol was necessary to aid in the dissolution of the Trolox®. To the control preparation was added 100 μL ethanol and 100 μL saline to account for the additional saline or ethanol added with the Trolox. Both vials were then reconstituted with 1.0 mL technetium ^{99m}Tc sodium pertechnetate (Technelite®) containing approximately 50 mCi ^{99m}Tc and allowed to incubate for 30 minutes at room temperature. Radiolabelling yield (RCP) results as measured by reversed phase HPLC are given in Table 17.

TABLE 17

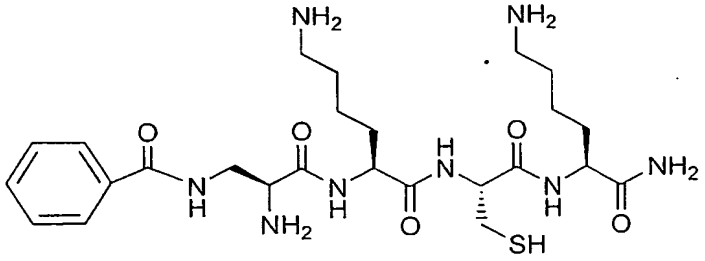
	HPLC RCP (%)		
Preparation	**0.5 hr**	**3.5 hr**	**6.5 hr**
Control	91.8	80.4	76.2
Trolox® (2 mg)	89.5	91.9	92.9

These results show that Trolox® increases the radiolabelling yield and the stability of ^{99m}Tc-peptide.

EXAMPLE 12

Stabilization of ^{99m}Tc-labelled Peptide Chelator by Trolox®

Trolox® was tested for its ability to stabilize a ^{99m}Tc-labelled monoamine, diamide, single thiol peptide chelator having the structure.



N-3-benzoyl-2,3-(S)-diaminopropionyl-L-lysinyl-L-cysteinyl-L-lysinyl amide

Lyophilized kit "placebo" vials were prepared containing sodium glucoheptonate dihydrate, edetate disodium dihydrate, and stannous chloride dihydrate at the concentrations set forth in Table 1 (control formulation).

The peptide chelator was radiolabelled with ^{99m}Tc in the presence and absence of Trolox®. The peptide chelator was dissolved in water at a concentration of 1 mg/mL, and 50 μg (50 μL) of the peptide was added to each of three placebo vials. Ethanol and Trolox® were added to the control and Trolox®, preparations as described in Example 11. In addition, 100 μL phosphate buffered saline (PBS) was added to each preparation. The vials were reconstituted with 0.9-1.0 mL ^{99m}Tc sodium pertechnetate (Technelite®) containing approximately 50 mCi ^{99m}Tc, and heated in a boiling water bath for ten

minutes. Radiolabelling yield (RCP) results as measured by reversed phase HPLC are given in Table 18.

TABLE 18

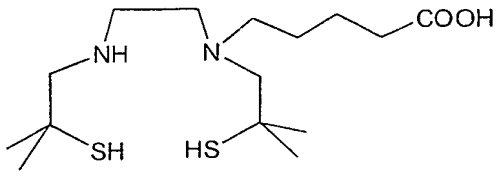
	HPLC RCP (%)			
Preparation	**0.5 hr**	**3 hr**	**6 hr**	**9 hr**
Control	94.1	92.4	85.9	80.0
Trolox® (2 mg)	95.3	95.4	91.5	86.4

These results show that Trolox® increases the radiolabelling yield and the stability of a ^{99m}Tc-labeled peptide chelator.

EXAMPLE 13

Stabilization of a ^{99m}Tc Bisamide Bisthiol Chelator by Trolox®

Trolox® was tested for its ability to stabilize a ^{99m}Tc-labelled non-peptide chelator (4-(butanoic acid)-2,2,9,9 tetramethyl-4,7-diaza-1,10-decanedithiol) having the structure.



The non-peptide chelator was radiolabelled with ^{99m}Tc in the presence and absence of Trolox® using the placebo vial heated preparation procedure as described in Example 11. Radiolabelling yield (RCP) results as measured by reversed phase HPLC are given in Table 19.

TABLE 19

	HPLC RCP (%)			
Preparation	**0.5 hr**	**3 hr**	**6 hr**	**9 hr**
Control	48.5	56.5	54.0	52.9
Trolox® (2 mg)	88.6	79.1	78.3	77.0

These results show that Trolox® increases the radiolabelling yield and the stability of a ^{99m}Tc-labelled non-peptide chelator.

EXAMPLE 14

Stabilization of ^{99m}Tc-labelled Depreotide by L-Methionine and Trolox®

Lyophilized kit vials were prepared containing depreotide, L-methionine (Met), Trolox®, and other components as described in Table 20. All formulations were adjusted to pH 7.4 prior to lyophilization.

TABLE 20

Component	Control	Trolox + Met
Depreotide	50 µg	50 µg
Sodium Glucoheptonate Dihydrate	5 mg	5 mg
Edetate Disodium Dihydrate	100 µg	100 µg
Stannous Chloride Dihydrate	50 µg	50 µg
Trolox	-	2 mg
L-Methionine	-	5 mg

The lyophilized kits were radiolabelled with ^{99m}Tc by reconstitution with 1.0 mL technetium ^{99m}Tc sodium pertechnetate (Technelite®) containing approximately 50 mCi ^{99m}Tc and incubation at room temperature for 30 minutes following reconstitution. Some of the formulations were also radiolabelled in a heated preparation (heat in a boiling water bath for 10 minutes). Radiolabelling yield (RCP) results as measured by reversed phase HPLC are given in Table 21.

TABLE 21

		HPLC RCP (%)		
Formulation	**Prep Type**	**0.5 hr**	**3.5 hr**	**6.5 hr**
Control	Heated	91.9	85.0	80.7
	Rm Temp	94.8	87.6	78.2
	Rm Temp	90.7	88.7	83.4
(Average):		(92.8)	(88.2)	(80.8)
Trolox (2 mg) + Met (5 mg)	Heated	92.0	93.4	94.1
	Heated	92.9	93.3	93.2
	Heated	93.6	90.7	91.5
(Average ± 1SD):		(92.8 ± 0.8)	(92.5 ± 1.5)	(92.9 ± 1.3)
	Rm Temp	85.1	78.6	83.2

These results indicate that the combination of L-methionine and Trolox® increases the radiolabelling yield and the stability of ^{99m}Tc depreotide prepared from formulated kits.

EXAMPLE 15

Stabilization of ^{99m}Tc Depreotide by L-Methionine and Trolox® in Lyophilized Kit Preparations; Accelerated Temperature (40°C) Storage

Lyophilized kits were prepared containing depreotide, L-methionine (Met) Trolox®, and other components as described in Table 20. All formulations were adjusted to pH 7.4 prior to lyophilization. The kits were stored for one week at 40°C. Some kits were also stored at -10°C as controls. The lyophilized kits were radiolabelled with ^{99m}Tc in heated preparations as set forth above. Radiolabelling yield (RCP) results as measured by reversed phase HPLC are given in Table 22.

TABLE 22

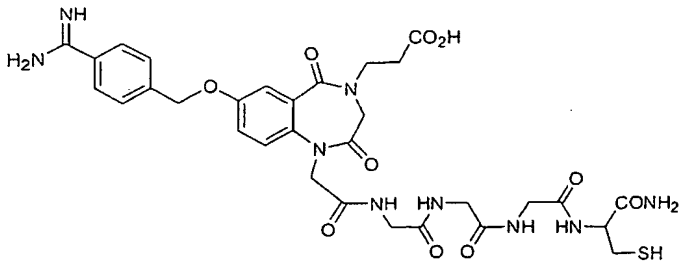
			HPLC RCP (%)[1]		
Formulation	Storage Temp	Prep Type	0.5 hr	3.5 hr	6.5 hr
Control	-10°C	Heated	-	82.6	77.8
	40°C	Heated	-	82.6	79.0
Trolox + Met	40°C	Heated	86.1	86.5	87.0

These results indicate that the combination of L-methionine and Trolox® stabilizes ^{99m}Tc-depreotide prepared from lyophilized kits which have been thermally stressed under conditions of accelerated temperature storage.

EXAMPLE 16

Stabilization of a ^{99m}Tc Benzodiazepinedione Derivative by L-Methionine and Trolox in Lyophilized Kit Preparations

L-methionine and Trolox® were tested for their ability to stabilize a glycoprotein IIb/IIIa receptor-binding benzodiazepinedione derivative 1-[(carboxyglycyl-glycyl-glycyl-cysteinamide)methyl]-4-(2-carboxyethyl)-7-[(4-amidinophenyl)methyl]-3,4-dihydro-1H-1,4-benzodiazepine-2,5-dione trifluoroacetate, having the structure.



Lyophilized kit vials were prepared containing the benzodiazepinedione derivative and components as described in Table 23. All formulations were adjusted to pH 7.4 prior to lyophilization.

TABLE 23

Component	Control	Trolox + Met
Derivative	40 μg	40 μg
Sodium Glucoheptonate Dihydrate	25 mg	25 mg
Edetate Disodium Dihydrate	100 μg	100 μg
Stannous Chloride Dihydrate	50 μg	50 μg
Trolox	-	2 mg
L-Methionine	-	5 mg

The lyophilized kits were radiolabelled with ^{99m}Tc by reconstitution with 1.0 mL technetium ^{99m}Tc sodium pertechnetate (Technelite®) containing approximately 50 mCi ^{99m}Tc and heating in a boiling water bath for 10 minutes. Radiolabelling yield (RCP) results as measured by reversed phase HPLC are given in Table 24.

TABLE 24

	HPLC RCP (%)		
Formulation	**0.5 hr**	**3.5 hr**	**6.5 hr**
Control	93.2	90.1	88.0
	93.6	94.5	88.8
	92.4	89.2	88.1
	85.0	86.1	82.3
(Average ± 1SD):	(91.0 ± 4.1)	(90.0 ± 3.5)	(86.8 ± 3.0)
Trolox (2 mg) + Met (5 mg)	92.5	92.9	90.3
	93.9	93.9	93.0
	94.1	93.6	90.9
(Average ± 1SD):	(93.5 ± 0.9)	(93.5 ± 0.5)	(91.4 ± 1.4)

These results indicate that the combination of L-methionine and Trolox® increases the radiolabelling yield and the stability of the ^{99m}Tc-labelled benzodiazepinedione derivative prepared from formulated kits.

It should be understood that the foregoing disclosure emphasizes certain specific embodiments of the invention and that all modifications or equivalents thereto are within the spirit and scope of the invention as set forth in the appended claims.

CLAIMS

1. A composition comprising a radiopharmaceutical precursor and a stabilizing amount of a stabilizer selected from the group consisting of:

(a) a hydrophilic thioether;

(b) a hydrophilic 6-hydroxy-chroman derivative; and

(c) a mixture of said thioether and said 6-hydroxy-chroman derivative.

2. The composition of claim 1, wherein the thioether is selected from the group consisting of D-methionine, L-methionine, 3-(methylthio)propionaldehyde, D-ethionine, L-ethionine, 3-methylthio-1,2-propanediol, methyl-3-(methylthio)propionate, 2-(ethylthio)ethylamine, 2-(methylthio)-ethanol, buthionine, S-methyl-L-cysteine, S-methyl-D-cysteine, D-methioninol, and L-methioninol.

3. The composition of claim 2, wherein the thioether is selected from the group consisting of D-methionine, L-methionine, 2-(ethylthio)ethylamine, D-methioninol, L-methioninol, and 3-methylthio-1,2-propanediol.

4. The composition of claim 3, wherein the thioether is L-methionine.

5. The composition of any of claims 1 through 4, wherein the hydrophilic 6-hydroxy-chroman is selected from the group consisting of 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid, 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid-4-sulfonic acid, 6-hydroxy-2,5,7,8-tetramethylchroman-3-hydroxy-2-carboxylic acid, 6-hydroxy-2,5,7,8-tetramethylchroman-2-glucosamine; and 6-hydroxy-2,5,7,8-tetramethylchroman-2-(carboxy-seryl-seryl-serylamide).

6. The composition of claim 5, wherein the hydrophilic 6-hydroxy-chroman is 6-hydroxy-2,5,7,8-tetramethyl-chroman-2-carboxylic acid.

7. The composition of any of claims 1 through 6, wherein the precursor comprises a targeting moiety selected from the group consisting of an antibody, a Fab antibody fragment, a $F(ab)'_2$ antibody fragment, an epitope binding complementarity determining region derived from an antibody, a peptide, a growth factor, a receptor binding fragment of a growth factor, a hormone, a steroid, a receptor binding nucleic acid, a receptor binding monosaccharide, a receptor binding disaccharide, a receptor binding oligosaccharide, a receptor-binding lipid, a receptor binding benzodiazepine derivative, and a receptor binding antibiotic.

8. The composition of claim 7, wherein the targeting moiety is a peptide.

9. The composition of claim 7, wherein the targeting moiety is a glycoprotein IIb/IIIa receptor-binding benzodiazepine derivative.

10. The composition of claim 7, wherein the targeting moiety is a receptor binding benzodiazepine derivative.

11. The composition of any of claims 1 through 6, wherein the precursor comprises a peptide chelator.

12. The composition of any of claims 1 though 6, wherein the precursor comprises a non-peptide chelator.

13. The composition of any of claims 1 through 12, further comprising a radionuclide.

14. The composition of claim 13, wherein the radionuclide is selected from the group consisting of ^{125}I, ^{131}I, ^{211}At, ^{47}Sc, ^{67}Cu, ^{72}Ga, ^{90}Y, ^{153}Sm, ^{159}Gd, ^{165}Dy, ^{166}Ho, ^{175}Yb, ^{177}Lu, ^{212}Bi, ^{213}Bi, ^{68}Ga, ^{99m}Tc, ^{111}In, and ^{123}I.

15. A composition according to any of claims 1 through 8, wherein the targeting moiety is a peptide selected from the group consisting of:

GGCSIPPEVKFNKPFVYLI.amide (SEQ ID NO:1);

GGCSIPPEVKFNKPFVYLI (SEQ ID NO:2);

GGCGLF (SEQ ID NO:3);

RGCSIPPEVKFNKPFVYLI.amide (SEQ ID NO:4);

RGCGHRPLDKKREEAPSLRPAPPPISGGYR.amide (SEQ ID NO:5);

GGCRPKPQQFFGLM.amide (SEQ ID NO:6);

GGCFVYLI.amide (SEQ ID NO:7);

(*acetyl*.TKPRGG)$_2$K(ε-K)GC.amide;

F_DFYW$_D$KTFT(ε-K)GC.amide;

acetyl.F_DFYW$_D$KTFT(ε-K)GC.amide;

acetyl.Nal$_D$.Cpa.YW$_D$KTFT(ε-K)GCKK.amide;

acetyl.F_DFYW$_D$KTFTGGG(ε-K)GC.amide;

acetyl.F_DFYW$_D$KTFTGGG(ε-K)KC.amide;

acetyl.KKKKK.Nal$_D$.Cpa.YW$_D$KTFT(ε-K)GC.amide;

acetyl.D_DF_D.Cpa.YW$_D$KTFT(ε-K)GCKK.amide;

acetyl.D_DF_D.Cpa.YW$_D$KTC(ε-K)GCKK.amide;

acetyl.KKKKK.Nal$_D$.Cpa.YW$_D$KTFT(ε-K)GCKK.amide;

acetyl.Nal$_D$.Cpa.YW$_D$KTFT(ε-K)GCKK.amide;

acetyl-DDD.Nal$_D$.Cpa.YW$_D$KTFT(ε-K)GCKK.amide;

acetyl.D_DDF_D.Cpa.YW$_D$KTFT(ε-K)GCKK.amide;

(DTPA).F_DFYW$_D$KTFT(ε-K)GC.amide;

(DTPA).Nal$_D$.Cpa..YW$_D$KT.Nal.T(ε-K)GCKK.amide;

(DTPA).(ε-K)GCF_DFYW$_D$KTFT.amide;

(DTPA).(ε-K)GCF_D.Cpa..YW$_D$KTFT.amide;

(DTPA).F_D.Cpa.YW$_D$KTFT(ε-K)GC.amide;

(DTPA).Nal$_D$.Cpa.YW$_D$KTFT(ε-K)GC.amide;

(DTPA).Aca.F_D.Cpa.YW$_D$KTFT(ε-K)GC.amide;

(DTPA).Nal$_D$.Cpa.YW$_D$KT.Nal.T(ε-K)GCKK.amide;

(DTPA).Nal$_D$.Cpa.YW$_D$KTFT(ε-K)GCKK.amide;

CH$_3$CO.FFW$_D$KTFC(ε-K)GC.amide;

CH$_3$CO.FFW$_D$KTFCKKKKK(ε-K)GC.amide;

CH$_3$CO.FFW$_D$KTFC(ε-K)KKKKKGC.amide;

AKCGGGF$_D$FYW$_D$KTFT.amide;

AKCGGGF$_D$YW$_D$KTFT.amide;

DDDD.Nal$_D$.Cpa.YW$_D$KTFT(ε-K)GCKKKK.amide;

DDD.Nal$_D$.Cpa.YW$_D$KTFT(ε-K)GCKK.amide;

Nal$_D$.Cpa.YW$_D$KTFT(ε-K)GCKK.amide;

Trc.Nal$_D$.Cpa.YW$_D$KTFT(ε-K)GCKK.amide;

Hca.Nal$_D$.Cpa.YW$_D$KTFT(ε-K)GCKK.amide;

(Trc)$_2$.Nal$_D$.Cpa.YW$_D$KTFT(ε-K)GCKK.amide;

KKKK.Nal$_D$.Cpa.YW$_D$KTFT(ε-K)GCDDDD.amide;

K$_D$.Nal$_D$.Cpa.YW$_D$KTFT(ε-K)GCD.amide;

K$_D$K.Nal$_D$.Cpa.YW$_D$KTFT(ε-K)GCDD.amide;

K$_D$KK.Nal$_D$.Cpa.YW$_D$KTFT(ε-K)GCDDD.amide;

K$_D$KK.Nal$_D$.Cpa.YW$_D$KTFT(ε-K)GCDD.amide;

K$_D$KKK.Nal$_D$.Cpa.YW$_D$KTFT(ε-K)GCDD.amide;

K$_D$KKK.Nal$_D$.Cpa.YW$_D$KTFT(ε-K)GCKDKD.amide;

K$_D$KKKF$_D$.Cpa.YW$_D$KTF,Nal.(ε-K)GCDDDD.amide;

K(BAT).Nal$_D$.C$_{Me}$YW$_D$KVC$_{Me}$T.amide

K$_D$DKD.Nal$_D$.Cpa.YW$_D$KTFT(ε-K)GCKDKD.amide;

KDKD.Nal$_D$.Cpa.YW$_D$KTFT(ε-K)GCKDKD.amide;

F$_D$.Cpa.YW$_D$KTC(ε-K)GCKK.amide;

F$_D$.Cpa.YW$_D$KTC(ε-K)GC.amide;

F$_D$.Cpa.YW$_D$KTFT(ε-K)GCKK.amide;

F$_D$.Cpa.YW$_D$K.Abu.Nal.T(ε-K)GC.amide;

F$_D$.Cpa.YW$_D$KTFTGGG(ε-K)GC.amide;

F$_D$.Cpa.YW$_D$KTFT(ε-K)GCR.amide;

(Trc-imide).Nal$_D$.Cpa.YW$_D$KTFT(ε-K)GCR.amide;

Trc.(Trc-imide).K.Nal$_D$.Cpa.YW$_D$KTFT(ε-K)GCRR.amide;

(Trc-imide)$_2$K.Nal$_D$.Cpa.YW$_D$KTFT(ε-K)GCRR.amide;

(Trc-imide)$_2$K.Nal$_D$.Cpa.YW$_D$KTFT(ε-K)GCR.amide;

D$_D$DF$_D$.Cpa.YW$_D$KTFT(ε-K)GCKK.amide;

D$_D$F$_D$.Cpa.YW$_D$KTFT(ε-K)GCKK.amide;

F$_D$FYW$_D$KTFT(ε-K)GCKK.amide;

AKCGGGF$_D$YW$_D$KTFT.amide;

(2-ketogulonyl).Nal$_D$.Cpa.YW$_D$KTFT(ε-K)GCKK.amide;

(2-ketogulonyl).F$_D$.Cpa.YW$_D$KTFT(ε-K)GC.amide;

cyclo-(*N*-CH$_3$)FYW$_D$KV.Hcy(CH$_2$CO.GC.Dap.Dap.amide);

cyclo.(*N*-CH$_3$)FYW$_D$KV.Hcy(CH$_2$CO.(γ-Dab)KCR.amide);

cyclo-(*N*-CH$_3$)FYW$_D$KV.Hcy(CH$_2$CO.KKKKK(ε-K)GC.amide);

cyclo-(*N*-CH$_3$)FYW$_D$KV.Hcy(CH$_2$CO).(ε-K)GCK.amide;

cyclo-(*N*-CH$_3$)FYW$_D$KV.Hcy(CH$_2$CO.(β-Dap)KCR.amide);

cyclo-(*N*-CH$_3$)FYW$_D$KV.Hcy(CH$_2$CO.(β-Dap)KCK.amide);

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cyclo-(*N*-CH$_3$)FYW$_D$KV.Hcy(CH$_2$CO.(β-Dap)GCK.amide);

cyclo-(*N*-CH$_3$)FYW$_D$KV.Hcy(CH$_2$CO.K(ε-K)KCK.amide);

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cyclo-(*N*-CH$_3$)FYW$_D$KV.Hcy(CH$_2$CO).K(ε-K)GC.amide;

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RGCQAPLYKKIIKKLLES (SEQ ID NO:8);

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acetyl.KKKKKK(ε-K)GCGGPLYKKIIKKLLES;

(CH$_2$CO.Y$_D$.Amp.GDC.KGCG.amide)$_2$(CH$_2$CO)$_2$K(ε-K)GC.amide;

(CH$_2$CO.Y$_D$.Amp.GDC.GGC$_{Acm}$GC$_{Acm}$GGC.amide)$_2$(CH$_2$CO)$_2$K(ε-K)GC.amide;

(CH$_2$CO.Y$_D$.Apc.GDCKGCG.amide)$_2$(CH$_2$CO)$_2$K(ε-K)GC.amide;

{(CH$_2$CO.Y$_D$.Apc.GDCGGCG.amide)(CH$_2$CO)}$_2$K(ε-K)GC.amide;

($CH_2CO.Y_D$.Apc.GDCKGG)$_2$K(ε-K)GC.β-Ala.amide;

($CH_2CO.Y_D$.Apc.GDCKKG)$_2$K(ε-K)GC.β-Ala.amide;

{($CH_2CO.Y_D$.Apc.GDCG)$_2$KG}$_2$.K(ε-K)GCG.amide;

($CH_2CO.Y_D$.Apc.GDC)$_2$K.(ε-K)GCG.amide;

({($CH_2CO.Y_D$.Apc.GDCGGC$_{Acm}$GC$_{Acm}$GGC.amide)(CH_2CO)}$_2$K)$_2$K(ε-K)GCG.amide;

{($CH_2CO.Y_D$.Apc.GDCGGC$_{Acm}$GC$_{Acm}$GGC.amide)$_2$(CH_2CO)$_2$K}$_2$K(ε-K)GCG.amide;

($CH_2CO.Y_D$.Apc.GDCGGC$_{Acm}$GC$_{Acm}$GGC.amide)$_2$(CH_2CO)$_2$K(ε-K)GC.amide;

HSDAVFTDNYTRLRKQMAVKKYLNSILN(ε-K)GC.amide;

HSDAVFTDNYTRLRKQMAVKKYLNSILNGGC.amide (SEQ ID NO:9);

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CH_2CO.SNLST.HcyVLGKLSC(CH_2CO.(ε-K)GCE.amide)ELHKLQTYPRTNTGSGTP.amide;

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CH_2CO.SNLST.CysVLGKLSC(CH_2CO.(β-Dap)KCK.amide)ELHKLQTYPRTNTGSGTP.amide;

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SNLST.AsuVLGKLSC(CH_2CO.(β-Dap)KCK.amide)ELHKLQTYPRTNTGSGTP.amide;

SNLST.AsuVLGKLSC(CH_2CO.(β-Dap)KCK.amide)ELHKLQTYPRTDVGAGTP.amide;

cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH_3)Hcy(CH_2CO-β-Dap-Tyr-Cys-Thr(ol));

cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH_3)Hcy(CH_2CO-β-Dap-Phe(4-F)-Cys-Thr(ol));

cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH_3)Hcy(CH_2CO-β-Dap-Phe(4-NH_2)-Cys-Thr-Ser);

cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH_3)Hcy(CH_2CO-β-Dap-Dab-Cys-Thr);

cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH_3)Hcy(CH_2CO-β-Dap-Phe(4-NH_2)-Cys-Thr);

cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH_3)Hcy(CH_2CO-β-Dap-Phe(4-NH_2)-Cys-Thr(ol));

cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH_3)Hcy(CH_2CO-β-Dap-His-Cys-Thr(ol));

cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH_3)Hcy(CH_2CO-β-Dap-Arg-Cys-Thr(ol));

cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH_3)Hcy(CH_2CO-β-Dap-Gly-Cys-Lys-NH_2);

cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH_3)Hcy(CH_2CO-β-Dap-Ser-Cys-Thr(ol));

cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH_3)Hcy(CH_2CO-β-Dap-Dab-Cys-Thr(ol));

cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH_3)Hcy(CH_2CO-β-Dap-Gly-Cys-Thr(ol));

cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH_3)Hcy(CH_2CO-β-Dap-Dab-Cys-Ser(ol));

cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH_3)Hcy(CH_2CO-Gly-Gly-Cys-Lys-NH_2);

cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH_3)Hcy(CH_2CO-Gly-Gly-Cys-Arg-NH_2);

cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH_3)Hcy(CH_2CO-Ser-Ser-Cys-Lys-NH_2);

cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH_3)Hcy(CH_2CO-Ser-Ser-Cys-Arg-NH_2);

cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH_3)Hcy(CH_2CO-Ser-Ser-Cys-Lys-Thr(ol));

cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH_3)Hcy(CH_2CO-Ser-Ser-Cys-Dap-NH_2);

cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH_3)Hcy(CH_2CO-Ser-Ser-Cys-$NH(CH_2CH_2O)_2CH_2CH_2NH_2$);

cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH_3)Hcy(CH_2CO-β-Dap-Ser-Cys-Thr-$NH(CH_2CH_2O)_2CH_2CH_2NH_2$);

cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH_3)Hcy(CH_2CO-Gly-Lys-Cys-NH_2);

cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH_3)Hcy(CH_2CO-Ser-Lys-Cys-NH_2);

cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH_3)Hcy(CH_2CO-Lys-Gly-Cys-NH_2);

cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH_3)Hcy(CH_2CO-Ser-Dab-Cys-Ser(ol));

cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH_3)Hcy(CH_2CO-Ser-Dap-Cys-NH_2);

cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH_3)Hcy(CH_2CO-Gly-Gly-Cys-His-NH_2);

cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH_3)Hcy(CH_2CO-Gly-Gly-Cys-Phe(4-NH_2)-NH_2);

cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH_3)Hcy(CH_2CO-β-Dap-Orn-Cys-Thr(ol));

cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH_3)Hcy(CH_2CO-β-Dap-Dap-Cys-Thr(ol));

cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH_3)Hcy(CH_2CO-β-Dap-Lys-Cys-Thr(ol));

cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH_3)Hcy(CH_2CO-Ser-Ser-Cys-$NHCH_2CH_2OCH_2CH_2NH_2$);

cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH_3)Hcy(CH_2CO-β-Dap-Lys-Cys-NH_2);

cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH_3)Hcy(CH_2CO-δ-Orn-Gly-Cys-NH_2); and

cyclo-Tyr-D-Trp-Lys-Thr-Phe-(N-CH_3)Hcy(CH_2CO-Thr-Gly-Gly-Cys-NH_2).

16. The composition of claim 15, wherein the stabilizer consists only of a thioether and said thioether is methionine.

17. The composition of claim 16, wherein the peptide is *cyclo*-(*N*-CH_3)FYW$_D$KV.Hcy(CH_2CO.(β-Dap)KCK.amide).

18. The composition of claim 16, wherein the peptide is *cyclo*-Tyr-D-Trp-Lys-Thr-Phe-(N-CH_3)Hcy(CH_2CO-β-Dap-Phe(4-NH_2)-Cys-Thr-Ser).

19. The composition of claim 15, wherein the stablizer consists only of a 6-hydroxy-chroman derivative and said 6-hydroxy-chroman derivative is 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid.

20. The composition of claim 19, wherein the peptide is *cyclo*-(*N*-CH_3)FYW$_D$KV.Hcy(CH_2CO.(β-Dap)KCK.amide).

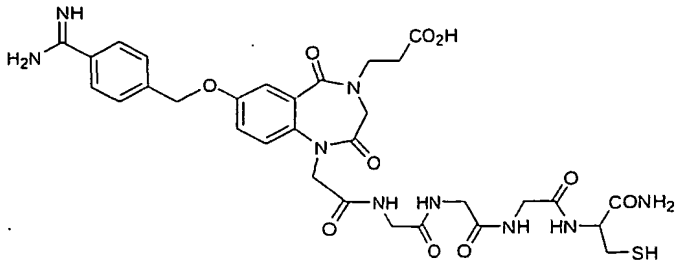
21. The composition of claim 15, wherein the stabilizer is a mixture of methionine and 6-hydroxy-2,5,7,8-tetramethyl-chroman-2-carboxylic acid.

22. The composition of claim 21 wherein the peptide is *cyclo*-(*N*-CH_3)FYW$_D$KV.Hcy(CH_2CO.(β-Dap)KCK.amide).

23. The composition of any of claims 15 through 22, further comprising a radionuclide.

24. The composition of claim 23, wherein the radionuclide is ^{99m}Tc. *cyclo*-(*N*-CH_3)FYW$_D$KV.Hcy(CH_2CO.(β-Dap)KCK.amide).

25. A composition comprising a hydrophilic thioether and a benzodiazepine derivative having a structure:

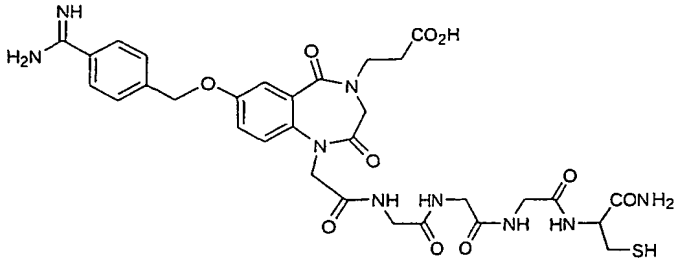


26. The composition of claim 25, wherein the thioether is methionine.

27. A composition comprising a hydrophilic 6-hydroxy-chroman derivative and 1-[(carboxyglycyl-glycyl-glycyl-cysteinamide)methyl]-4-(2-carboxyethyl)-7-[(4-amidinophenyl)methyl]-3,4-dihydro-1H-1,4-benzodiazepine-2,5-dione trifluoroacetate.

28. The composition of claim 27, wherein the hydrophilic 6-hydroxy-chroman derivative is 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid.

29. A composition comprising a hydrophilic thioether, a hydrophilic 6-hydroxy-chroman derivative, and a benzodiazepine derivative having a structure:



30. The composition of claim 29, wherein the thioether is methionine and the hydrophilic 6-hydroxy-chroman derivative is 6-hydroxy-2,5,7,8-tetramethyl-chroman-2-carboxylic acid.

31. The composition of any of claims 25 through 30, further comprising ^{99m}Tc.

32. A method of stabilizing a radiopharmaceutical comprising the steps of:

a) combining a precursor of said radiopharmaceutical with a stabilizing amount of a hydrophilic thioether in a container; and

b) adding a radionuclide to the container.

33. The method of claim 32, wherein the thioether is methionine.

34. A method of stabilizing a radiopharmaceutical comprising the steps of:

a) combining a precursor of said radiopharmaceutical with a stabilizing amount of a hydrophilic 6-hydroxy-chroman derivative in a container; and

b) adding a radionuclide to the container.

35. The method of claim 34, wherein the hydrophilic 6-hydroxy-chroman derivative is 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid.

36. A method of stabilizing a radiopharmaceutical comprising the steps of:

a) combining a precursor of said radiopharmaceutical with a stabilizing amount of a mixture of a hydrophilic thioether and a hydrophilic 6-hydroxy-chroman derivative in a container; and

b) adding a radionuclide to the container.

37. The method of claim 36, wherein the thioether is methionine and the hydrophilic 6-hydroxy-chroman derivative is 6-hydroxy-2,5,7,8-tetramethyl-chroman-2-carboxylic acid.

38. The method of any of claims 32 through 37, wherein the radionuclide is ^{99m}Tc.

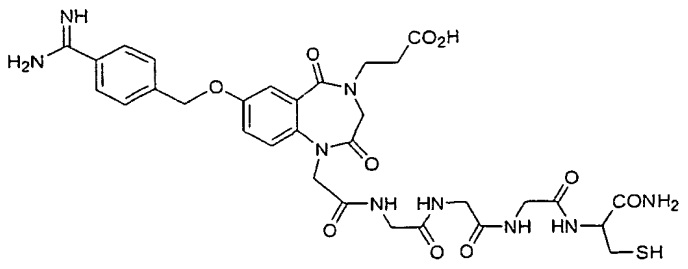
39. A kit comprising a sealed vial containing a predetermined quantity of a radiopharmaceutical precursor and a stabilizing amount of a hydrophilic thioether.

40. The kit of claim 39, wherein the thioether is methionine.

41. The kit of claim 40, wherein the precursor is *cyclo*-(*N*-CH_3)FYW$_D$KV.Hcy(CH_2CO.(β-Dap)KCK.amide).

42. The kit of claim 40, wherein the precursor is *cyclo*-Tyr-D-Trp-Lys-Thr-Phe-(N-CH_3)Hcy(CH_2CO-β-Dap-Phe(4-NH_2)-Cys-Thr-Ser).

43. The kit of claim 40, wherein the precursor is



44. A kit comprising a sealed vial containing a predetermined quantity of a radiopharmaceutical precursor and a stabilizing amount of a hydrophilic 6-hydroxy-chroman derivative.

45. The kit of claim 44, wherein the hydrophilic 6-hydroxy-chroman derivative is 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid.

46. The kit of claim 45, wherein the precursor is *cyclo*-(*N*-CH_3)FYW$_D$KV.Hcy(CH_2CO.(β-Dap)KCK.amide).

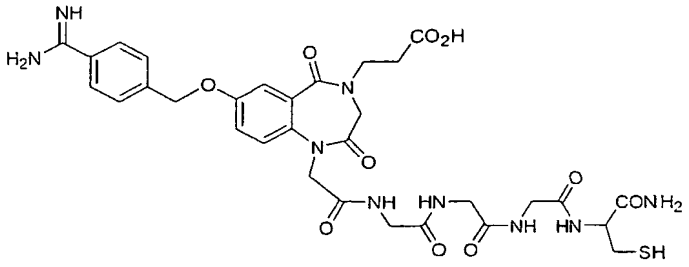
47. The kit of claim 45, wherein the precursor is: 1-[(carboxyglycyl-glycyl-glycyl-cysteinamide)methyl]-4-(2-carboxyethyl)-7-[(4-amidinophenyl)methyl]-3,4-dihydro-1H-1,4-benzodiazepine-2,5-dione trifluoroacetate.

48. A kit comprising a sealed vial containing a predetermined quantity of a radiopharmaceutical precursor and a stabilizing amount of a mixture of a hydrophilic thioether and a hydrophilic 6-hydroxy-chroman derivative

49. The kit of claim 48, wherein the thioether is methionine and the hydrophilic 6-hydroxy-chroman derivative is 6-hydroxy-2,5,7,8-tetramethyl-chroman-2-carboxylic acid.

50. The kit of claim 49, wherein the precursor is *cyclo*(*N*-CH_3)FYW$_D$KV.Hcy.(CH_2CO.(β-Dap)KCK.amide).

51. The kit of claim 49, wherein the precursor is



SEQUENCE LISTING

<110> Cyr, John
Pearson, Daniel

<120> STABILIZATION OF RADIOPHARMACEUTICAL COMPOSITIONS USING HY DROPHILIC THIOETHERS AND HYDROPHILIC 6-HYDROXY CHROMANS

<130> DITI 133

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<141> 2000-10-23

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: STABILIZATION OF RADIOPHARMACEUTICAL COMPOSITIONS USING HYDROPHILIC THIOETHER OR A HYDROPHILIC 6-HYDROXY CHROMAN

(57) Abstract: Radiopharmaceutical compositions which are stabilized by addition of a hydrophilic thioether, a hydrophilic 6-hydroxy-chroman derivative, or a mixture of a hydrophilic thioether and a hydrophilic 6-hydroxy-chroman derivative. specific hydrophilic thioethers of the present invention include D-methiionine, L-methionine, D-ethionine, L-ethionine, 3-methylthio-1,2-propanediol, methyl-3-(methylthio)propionate, 2-(ethylthio)ethylamine•HC1,2-(methylthio)-rthanol, buthionine, S-methyl-L-cysteine, S-methyl-D-cysteine, D-methioninol, L-methioninol, and the like. Preferably, the hydrophilic thioether used in the compositions of the invention is methioninol, 2-(ethylthio)-ethylamine•HC1,3-methythio-1,2-propanediol, or methionine. More preferably, the hydrophilic thioether used in the compositions of the invention is 2-(ethylthio)-ethylamine•HC1 or methionine. Exemplary hydrophilic 6-hydroxy-chroman derivatives of the present invention include 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid (Trolox ®, available from Aldrich Chemical Co., (milwaukee, Wisconsin, USA);6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid-4-sulfonic acid; 6-hydroxy-2,5-7,8-tetramethylchroman-3-hydroxy-2-carboxylic acid; 6-hydroxy-2,5,7,8-tetramethylchroman-2-glucosamine, and 6-hydroxy-2,5,7,8-tetramethylchroman-2-(carboxy-seryl-serylamide). preferably, the hydrophilic 6-hydroxy-chroman derivative of the present invention is a water soluble vitamin E derivative.

WO 02/060491 A3

INTERNATIONAL SEARCH REPORT

Intern Application No
PCT/US 01/50423

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K51/12 //A61K103:10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, EMBASE, BIOSIS, MEDLINE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 37 22 647 A (OHLENSCHLAEGER GERHARD) 19 January 1989 (1989-01-19) abstract	1,39,40
X	WO 95 01188 A (RHOMED INC) 12 January 1995 (1995-01-12) page 25, line 13-26 -page 26, line 1-3	1,14,15, 32,39
X	WO 00 61195 A (DIATIDE INC ;GENENTECH INC (US)) 19 October 2000 (2000-10-19) example 3 claims 1-25	1-4, 14-18, 32,33, 39-42

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 April 2003	13. 08. 2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Vadot, P

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

In ional application No.
PCT/US 01/50423

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 7-13
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-4, 14, 15-18, 32-33, 39-42 (all partially)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 7-13

Present claims 1,7-12 relates to compounds defined by reference to a desirable characteristic or property, namely :
- a radiopharmaceutical precursor
- a hydrophilic thioether
- a hydrophilic 6-hydroxy-chroman derivative

The claim cover all compounds having these characteristics or properties, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claim also lack clarity (Article 6 PCT). An attempt is made to define the compounds by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds :
claims 2,3,15.

Furthermore, present claims 7-13 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely a peptide of claims 15 comprising a targeting moiety and a chelation site, stabilized by a thioether of claim 2; this peptide being tagged by 99Tc.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: (1-4,14,15-18, 32-33,39-42)partially

   Hydrophilic thioether (L-Methionine) as stabilizer of a peptide chelator with a peptide as a targeting moiety.

2. Claims: (1-4,14,16-18,21-31,34,36-44,47-51, 32,33)partially

   Hydrophilic thioether (L-Methionine) as stabilizer of a peptide chelator with a glycoprotein IIb/IIIa receptor-binding benzodiazepin derivative.

3. Claims: (1-4,14,16-18,21-24,29-31,34,36-38,41,42,44,46, 48-51, 25,26,32,33,39,40,43)partially

   Hydrophilic thioether (L-Methionine) as stabilizer of a peptide chelator with receptor-binding benzodiazepin derivative.

4. Claims: (1-4,14,16,21,23-25,29-31,34,36-38,44,48,49, 32,33, 39,40)partially

   Hydrophilic thioether (L-Methionine) as stabilizer of a non-peptide chelator with a peptide as targeting moiety.

5. Claims: (1-4,14,16,21,23-27,29-31,34,36-38,44,48,49, 32,33, 39,40)partially

   Hydrophilic thioether (L-Methionine) as stabilizer of a non-peptide chelator with a glycoprotein IIb/IIIa receptor -binding benzodiazepin derivative.

6. Claims: (1-4,14,16, 21.23-26.29-31.34.36-38.43.44.48- 49.32.33.39.40)partially

   Hydrophilic thioether (L-Methionine) as stabilizer of a non-peptide chelator with a receptor-binding benzodiazepin derivative.

7. Claims: (1,5,6, 14.15.17-32.36-39.41-43.46.48-

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

51.34.35.44.45)partially

Hydrophilic 6-hydroxy-chroman (trolox(R)) as stabilizer of a peptide chelator with a peptide as a targeting moiety.

8. Claims: (1.5.6.14.15.17-24.29-32.36-39.41-43.46.48-51.
27.28.34.35.44.45.47)partially,

Hydrophilic 6-hydroxy-chroman (trolox(R)) as stabilizer of a peptide chelator with a glycoprotein IIb/IIIa receptor -binding benzodiazepin derivative.

9. Claims: (1.5.6.14.15.17-25.27-32.34-39.41-43.46-
50.34.35.44.45.51)partially

Hydrophilic 6-hydroxy-chroman (trolox(R)) as stabilizer of a peptide chelator with a receptor-binding benzodiazepin derivative.

10. Claims: (1.5.6.14.15.17-25.27-32.36-39.41.42.46-
51.34.35.44.45)partially

Hydrophilic 6-hydroxy-chroman (trolox(R)) as stabilizer of a non-peptide chelator with a peptide as targeting moiety.

11. Claims: (1.5.6.14.19.21-24.27-32.36-39.47-
49.34.35.44.45)partially

Hydrophilic 6-hydroxy-chroman (trolox(R)) as stabilizer of a non-peptide chelator with a glycoprotein IIb/IIIa receptor -binding benzodiazepin derivative.

12. Claims: (1.5.6.14.19.21.23-25.27-32.36-
39.43.45.45.45.51.34.35.44)partially

Hydrophilic 6-hydroxy-chroman (trolox(R)) as stabilizer of a non-peptide chelator with a receptor-binding benzodiazepin derivative.

13. Claims: (1-6.14-35.37-47.49.36.48.50)partially

Hydrophilic thioether and hydrophilic 6-hydroxy-chroman (trolox(R)) as stabilizers of a peptide chelator with a

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

peptide as targeting moeity.

14. Claims: (1-6.14-35.37-51.36.48)partially

Hydrophilic thioether and hydrophilic 6-hydroxy-chroman (trolox(R)) as stabilizers of a peptide chelator with a glycoprotein IIb/IIIa receptor-binding benzodiazepin derivative as targeting moeity.

15. Claims: (1-6.14-35.37-47.49-51.36.48)partially

Hydrophilic thioether and hydrophilic 6-hydroxy-chroman (trolox(R)) as stabilizers of a peptide chelator with a receptor-binding benzodiazepin derivative as targeting moeity.

16. Claims: (1-6.14.16-23.26-35.37-46.49-51.36.48)partially

Hydrophilic thioether and hydrophilic 6-hydroxy-chroman (trolox(R)) as stabilizers of a non-peptide chelator with a peptide as targeting moeity.

17. Claims: (1-6.14.16.19.21.23-35.37-40.44.45.49.36.48)partially

Hydrophilic thioether and hydrophilic 6-hydroxy-chroman (trolox(R)) as stabilizers of a non-peptide chelator with a glycoprotein IIb/IIIa receptor-binding benzodiazepin derivative as targeting moeity.

18. Claims: (1-6.14-16.19.21.23-35.37-40.44.45.49.36.48)partially

Hydrophilic thioether and hydrophilic 6-hydroxy-chroman (trolox(R)) as stabilizers of a non-peptide chelator with a receptor-binding benzodiazepin derivative as targeting moeity.

INTERNATIONAL SEARCH REPORT

Intern Application No
PCT/US 01/50423

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